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A CLASSIFICATION OF THE TUMORS OF THE GLIOMA GROUP ON A HISTOGENETIC BASIS WITH A CORRELATED STUDY OF PROGNOSIS

A CLASSIFICATION OF THE TUMORS OF THE GLIOMA GROUP ON A HISTOGENETIC BASIS WITH A CORRELATED STUDY OF PROGNOSIS

BY

PERCIVAL BAILEY AND HARVEY CUSHING

FROM THE SURGICAL CLINIC AND LABORATORY OF
THE PETER BENT BRIGHAM HOSPITAL AND THE
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HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS

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DEDICATED
TO
PROFESSOR S. RAMÓN Y CAJAL
AND THE DISTINGUISHED DISCIPLES
OF HIS SCHOOL OF
SPANISH NEUROHISTOLOGISTS

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A CLASSIFICATION OF THE TUMORS OF THE GLIOMA GROUP ON A HISTOGENETIC BASIS WITH A CORRELATED STUDY OF PROGNOSIS

A. INTRODUCTION

The impression prevails in both laboratory and clinic that the microscopical examination of a specimen removed at operation will not serve to predict, with any degree of certainty, the future course of development of a true tumor of the brain substance. These lesions, which are commonly grouped together as gliomas, represent about 40 per cent. of all intracranial neoplasms. They exhibit a bewildering variety of microscopical structure, and existing classifications have served to do little more than add confusion to a complicated subject.

A reasonable promise of bringing some order out of this chaos could only be possible in a clinic where the specimens and records are available from a sufficiently large series of cases—cases, moreover, which have been observed over a long period of years and which have been followed carefully from the onset of symptoms to the death of the patient. Taking advantage of such an opportunity, the authors some years ago began an investigation of the histopathology and histogenesis of these tumors, posing for themselves the following questions: (1) What is the basis of the structural variability shown by these gliomatous tumors? (2) Has their histological variation any clinical significance? and (3) Does it account for the unexpectedly long survival period, or even cure, after extirpating certain of them?

There have been available for our purposes the material and records of over 400 " verified gliomas," including 167 necropsy specimens, collected in part at the Johns Hopkins Hospital and later at the Peter Bent Brigham Hospital, covering the period of 21 years from January 1, 1903, to January 1, 1924. The attempt has been made to arrange and to classify the material in a way which should be at once logical, understandable, and useful. Studies on similar lines have been made by Tooth,[69] by Greenfield,[26] and by Roussy, Lhermitte, and Cornil,[62] but modern impregnation methods were not employed by these writers, nor was sufficient stress laid by them, in our opinion, upon the correlation of clinical data with the pathological findings.

Our research, little more than the bare results of which are herein reported, has been made possible by the generosity of others. It would have been beyond our resources to have undertaken a piece of work on so large a scale had it not been that a fund for the study of brain tumors had been put at our disposal by the heirs of Mr. Philip H. Gray, who died in the Brigham Hospital in November of 1922, several months after a futile operation for a malignant glioma of the corpus callosum. We wish to acknowledge also the generosity of our colleagues in Pathology. The senior author, while at the Johns Hopkins, was given the privilege, by Professor Welch and the members of his department, not only of making his own post-mortem examinations of the neurological cases he had operated upon with fatal issue, but at the same time, so long as proper pathological reports were submitted for the purpose of record, of retaining the specimens. No experience for a surgeon in a comparatively new field could possibly have been more valuable and informing.

In later years at the Brigham Hospital, Professor Councilman and his successor, Professor Wolbach, in spite of their personal great interest in the subject, have been no less considerate in surrendering the immediate supervision of this most precious pathological material. The authors have a strong conviction that except in the case of standard and long-established procedures, surgical therapeutics can be best advanced if the surgeon assumes full responsibility not only for the preliminary bedside studies and diagnoses which precede his operations, but also for the post-operative laboratory examination of the tissues which follow them. If this responsibility is divided, as it customarily is divided, between the physician (or neurologist in the case before us), surgeon, and pathologist, the surgeon is prone to deteriorate into a mere handicraftsman who leaves to others the more intellectual parts of his work. Under such an arrangement, the material is not likely ever to be thoroughly studied from all points of view; the neurosurgeon is not likely to exercise the kind of judgment which only comes from seeing all round his subject; and, finally, with responsibilities divided, no one is sufficiently interested to engage in the arduous task of keeping in touch with the patients to their end.

B. HISTOGENESIS OF THE BRAIN

THE histogenesis of the brain furnishes the indispensable background for an understanding of its tumors. There are unfortunately many gaps in our knowledge of the subject; but a few excellent investigations of short developmental stages or of a particular line of cellular differentiation are available, and upon them is based the following incomplete and necessarily, in part, hypothetical account. It is introduced here for the sake of reference, although much of it is a mere repetition of what is widely known.

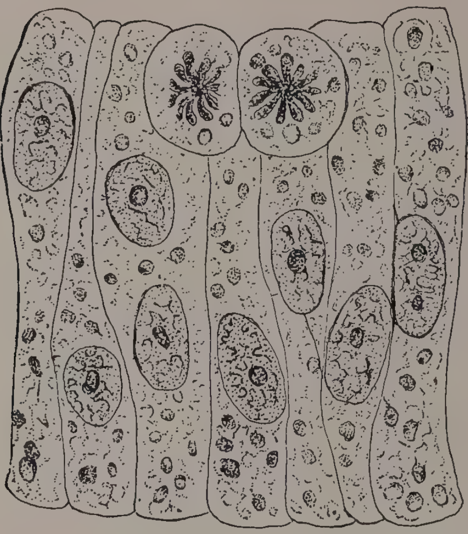
FIG. 1.—Medullary epithelium. Two germinal cells above. (After His.)

The anlage of the central nervous system is differentiated early in embryonic life from the ectoderm along the axial line. There is no need to describe how this long strip of ectoderm becomes thickened to form the medullary plate and how its middle portion is depressed to form the medullary groove. Suffice it to say that the elevated edges of the groove come together and fuse, converting it into the medullary tube, the anterior portion of which becomes enlarged and subdivided by constrictions into the three primary vesicles of the brain.

At first the medullary plate is composed of a single layer of columnar epithelial cells which may be called the *medullary epithelium.* While the medullary plate is in the process of being transformed into the medullary tube an active proliferation of these cells occurs, and the simple primitive arrangement is in some portions lost. By the continued division and differentiation of the cells the enormously complicated structure of the brain finally comes into existence.

The earliest sign of differentiation is the appearance within the medullary epithelium of round vesicular cells in mitosis (Fig. 1). They are known as germinal cells, and from them neuroblasts are differentiated, as was first clearly demonstrated by His.[32] These germinal cells continue to multiply between the external and internal limiting membranes of the medullary tube. They elongate the remaining epithelial cells and separate them from each other in their outer portions, thus transforming them into what Castro [11] has called primitive spongioblasts (Fig. 2). Some of the germinal cells differentiate at once, but others continue to divide, giving rise to new generations of undifferentiated cells known as indifferent cells (Schaper [64]), a term which implies that one is unable to predict what they will become in their future development. We prefer to speak of these indifferent cells as *medulloblasts.*[3]

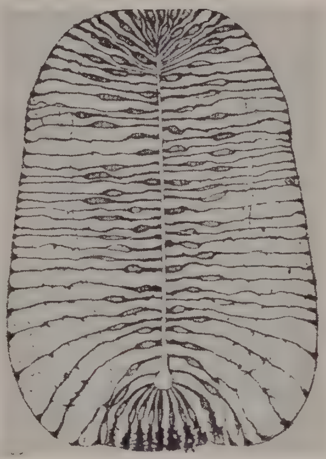

Fig. 2.—Primitive spongioblasts of spinal cord. Chick embryo on third day of incubation. Golgi's method. (After Cajal.)

At this early stage of development one may recognize in the medullary tube three types of cells: (1) the *primitive spongioblasts* already mentioned as elongated cells separated at their outer extremities by the proliferation of germinal cells, and reaching from the internal to the external limiting membranes; (2) the *medulloblasts* or indifferent cells, which are small and show a scanty cytoplasm in a narrow ring around the nucleus; and (3) the *neuroblasts.*

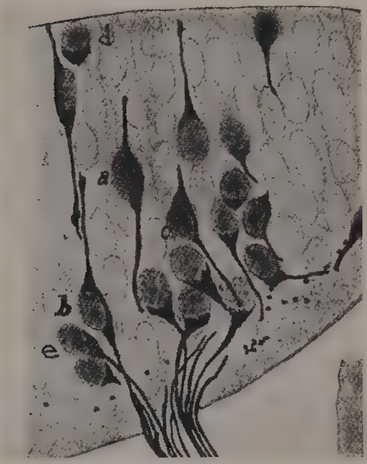

Fig. 3.—Neuroblasts in the ventral part of the medullary tube 1 cm. pig embryo. Pyridine-silver method. (After Held.) a, b, c, bipolar; d, apolar; e, unipolar.

THE NEUROBLASTS.—These arise only from the germinal cells, as His first pointed out, though the details of their differentiation have since been thoroughly investigated by Hans Held[30] and by S. Ramón y Cajal.[10] When the neuroblast first makes its appearance it is a globular cell with a nucleus not essentially different from those of the surrounding primitive spongioblasts. Its cytoplasm is collected toward one pole of the cell, and has a marked affinity for reduced silver. At this stage it is known, in accordance with Held's description, as an *apolar* neuroblast (Fig. 3, d). The cytoplasm increases rapidly in amount, and from the argentophilic area processes are at first put out in two opposite directions, so that a bipolar cell results (Fig. 3, a and Fig. 4, d); but soon one process is withdrawn, and the cell assumes a piriform shape with a single long process coming from the smaller end (Figs. 3, e and 4, e). This process contains fine fibrillæ which attract reduced silver with great avidity. It is in this stage that the cell is commonly known as a neuroblast (His), or, to be more exact, as a *unipolar* neuroblast.

Shortly after the initiation of this unipolar stage the nucleus of the neuroblast begins to enlarge markedly (Fig. 5); it becomes vesicular and its chromatin collects into one or two heavy nucleoli. The centrosome becomes extruded into the periphery of the cytoplasm, where it can be found (Hortega) only with the greatest difficulty.

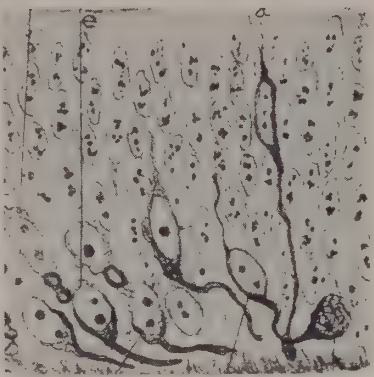

Fig. 4.—Neuroblasts in the lumbar cord of the chick. Third day of incubation. Reduced silver method. (After Cajal.) d, bipolar; e, unipolar.

In its further development the neuroblast puts out multiple processes in various directions and becomes known as a *multipolar* neuroblast (Fig. 6, b). These processes increase in length and complexity until the final transformation into an adult *neurone* is marked by the deposition of the tigroid substance in the cytoplasm, which takes place in the human embryo of 20–30 mm. crown-rump length, and by the deposition of myelin around the axis cylinder in the second half of intra-uterine life.*

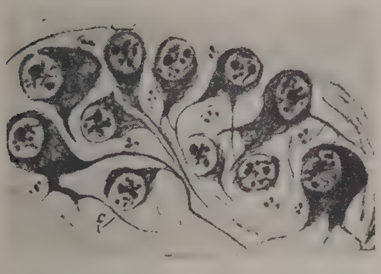

Fig. 5.—Neuroblasts in the superior cervical ganglion of the human foetus of six months. Note distinction between nuclei of neuroblasts and neuroglia. Reduced silver method. (After Castro.)

The Primitive Spongioblasts.—These cells meanwhile are not inactive. Their transformations have been followed by

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* The foregoing description is fairly true for the cerebral vesicles. Many variations occur, especially in the peripheral nervous system. The bipolar stage may follow the unipolar stage; the unipolar stage may never develop; the nuclear transformation may never occur, as in the case of the granule cells of the cerebellum or the bipolar cells of the retina; the centrosome may persist in the centre of the cytoplasm as in the sympathetic ganglion cells, etc.

Castro[11] in the olfactory bulbs, and his account may be taken as indicative of what happens elsewhere. The primitive spongioblasts can be soon identified by their specific affinity for gold-sublimate and for Golgi's chromate. Their ventricular ends are ciliated, and, as His first pointed out, blepharoplasten in the form of diplosomes appear at the base of each cilium after the fifth week of development. Their nuclei are oval, with a heavily reticulated chromatinic network. They may be divided into two types (Fig. 7): (1) those in which the nucleus with the bulk of the cytoplasm lies near the ventricle, the future ependymal cells; and (2) those in which the nucleus with most of the cytoplasm lies remote from the ventricle, the precursors of neuroglia cells, which have a thick process extending to the inner ventricular surface. The outer extremities of both types continue off in long tails to the external limiting membrane. The picture is familiar from the early researches of Golgi, and of Cajal, Retzius, and others, who subsequently employed his methods (*cf.* Fig. 2). Even in the adult central nervous system cells remain in this primitive stage in the region of the roof- and floor-plates of the medullary tube. Elsewhere,

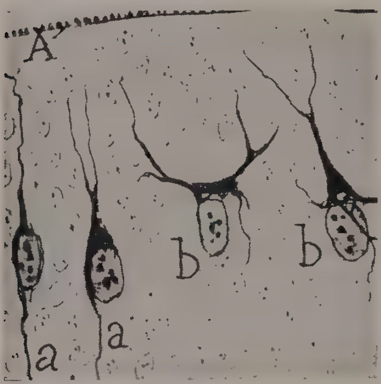


Fig. 6.—Neuroblasts in retina of rat recently born. Reduced silver method. (After Cajal.) a, a, bipolar; b, b, multipolar.

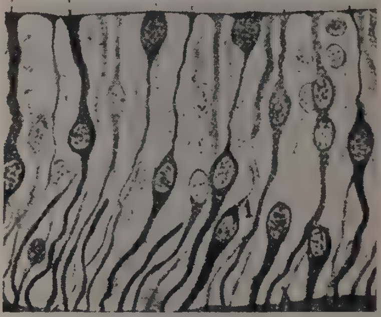


Fig. 7.—Primitive spongioblasts in the olfactory bulb of recently born dog. Gold-sublimate method. (After Castro.) 1, bipolar form.

especially in the region of the cerebral hemispheres, a further and complicated transformation of the primitive spongioblasts occurs. They divide by amitotic division, giving rise to *bipolar* spongioblasts (Fig. 7).

Bipolar spongioblasts may also arise by the migration of the 'type 1' cells away from the internal limiting membrane. When this occurs the internal process atrophies, the connection with the external limiting membrane is lost, and the spongioblast lies free in the tissue of the wall of the medullary tube. The spongioblast in this stage is designated by Castro a "dislocated epithelial corpuscle," but it is perhaps simpler to call it a *unipolar* spongioblast (Fig. 8). Early investigators undoubtedly often confused these cells with unipolar neuroblasts because of the fact that each, when impregnated by Golgi's method, shows a similar silhouette.

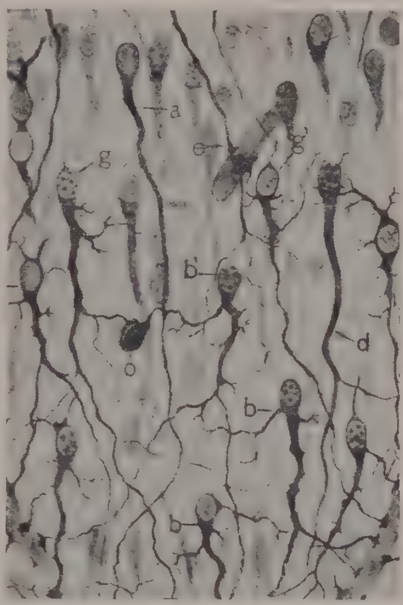


Fig. 8.—Unipolar spongioblasts in the olfactory bulb of recently born dog. Gold-sublimate method. (After Castro.) a, unipolar type; e, process acquiring attachment to capillary wall.

The unipolar spongioblast, then, is a piriform cell, with a long process, coming from the smaller end, which does not attract reduced silver, but does attract gold-sublimate. At the base of the process lies the centrosome in the form of a single heavy granule surrounded by a clear zone.

Medulloblasts (Indifferent cells).—The origin of the unipolar spongioblasts from the medullary epithelium was first described by His,[32] but he was careful to point out that spongioblasts might possibly arise also from germinal cells. Since he could find no transitional stages between germinal cells and spongioblasts, he held such an origin as unproven. Schaper [64] first called attention to the fact that a single origin from the medullary epithelium alone was insufficient to account for the great numbers of spongioblasts in the developing central nervous system, even though it was known that the latter continued to divide amitotically. He therefore proposed the formal hypothesis that the germinal cells did not necessarily differentiate into neuroblasts, but might continue to divide on an undifferentiated plane of development, and eventually become either spongioblasts or neuroblasts. This view was later accepted by His,[31] with the theoretical reservation that he did not believe, as did Schaper, that the indifferent cells were bipotential and, under external influences, could become either spongioblasts or neuroblasts. He believed rather that each cell was unipotential and was predestined from the beginning to become a neuroblast or a spongioblast, as the case might be, but that in the indifferent stage there was no means of determining the actual potentiality of any given cell.

We have, as a matter of fact, no means of identifying these medulloblasts except by negative characteristics, but Schaper's hypothesis, which is generally accepted, is necessary to a comprehension of the normal histogenesis of the brain (Cajal), of malformations of the brain (Monakow), and, as will appear in the present work, for an understanding of brain tumors. We must accept, then, as a working hypothesis the presence in the developing encephalon of large numbers of migrating undifferentiated cells which divide actively and may later differentiate into neuroblasts, into spongioblasts, or remain fixed in their undifferentiated stage of development.

Astroblasts.—The unipolar spongioblasts, of whatever origin, undergo a further transformation. Their tails become attached to the walls of capillaries (Fig. 8) and the cell then begins to develop processes which extend in various directions out from the perinuclear cytoplasm. In this stage it is known as an *astroblast* (Fig. 9), distinguished by a broad process attached to the wall of a blood-vessel, where it becomes enlarged into what is known as the " sucker foot," and by short stubby processes which extend in many directions from the opposite pole of the cell.

Neuroglia-fibrils begin to develop in the cytoplasm of the astroblasts during this stage, which is about the fourth month of intra-uterine life. Not in all the astroblasts do fibrils develop, and therein arises the distinction between the *fibrillary astrocytes* of the marginal and subcortical regions, and the *protoplasmic astrocytes* of the cortex. The protoplasmic and fibrillary astrocytes together compose the *neuroglia.*

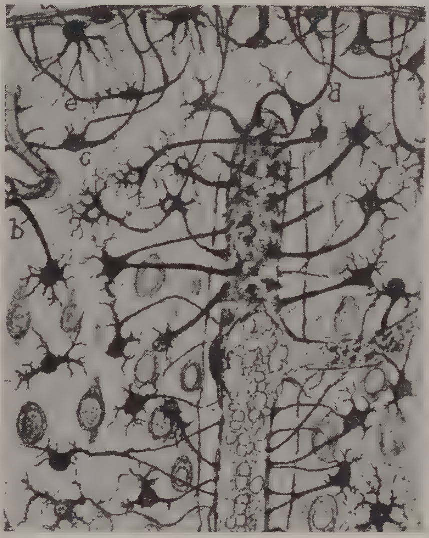


Fig. 9.—Astroblasts in cerebrum of fifteen-day cat. Gold-sublimate method. (After Cajal.)

Protoplasmic Astrocytes.—These protoplasmic neuroglia-cells (Fig. 10, a), as told in Cajal's original description,[9] are found in the middle and deeper layers of the cerebral cortex, and also in the molecular layer of the cerebellum. They may be roughly subdivided into: (1) bulky cells rich in cytoplasm and having large processes; (2) smaller ones with fewer appendices; and (3) satellite or perineuronal cells.

The nuclei of all these cells are rather large and oval, possessing many coarse chromatin granules united by heavy linin cords (Fig. 13, b). In the cytoplasm of the larger cells may be distinguished an endoplasm and an ectoplasm. The ectoplasm, which stains much more heavily, is continuous with the processes. The smaller cells seem to be composed wholly of ectoplasm.

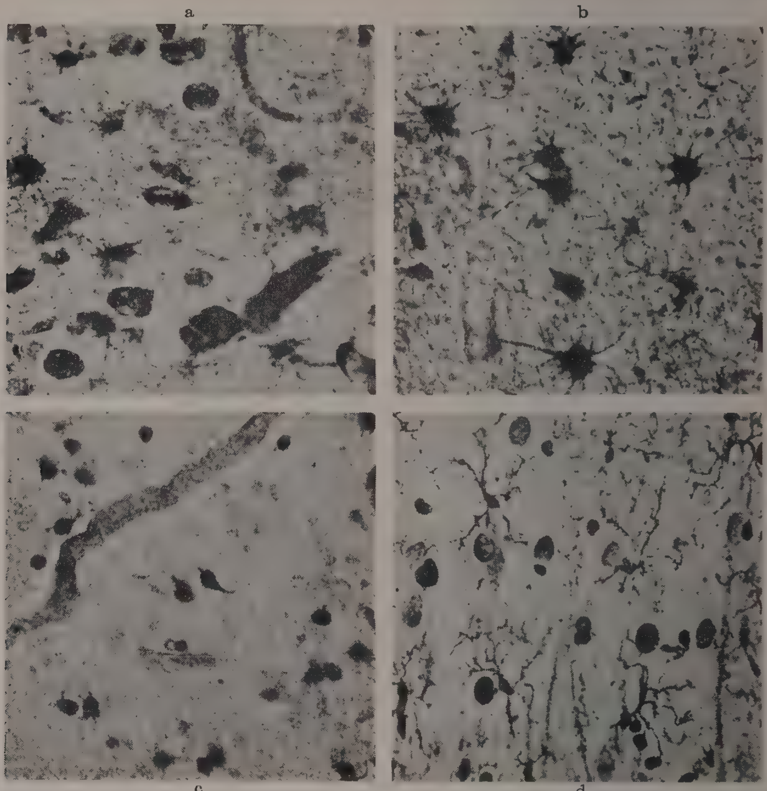


Fig. 10.—a, Protoplasmic astrocytes. Human cerebral cortex. Gold-sublimate method. × 300. b, Fibrillary astrocytes. Human cerebral subcortex. Gold-sublimate method. × 300. c, Oligodendroglia. Cerebral cortex of dog. Robertson's platinum chloride method. × 300. d, Microglia. Cerebral cortex of rabbit. Hortega's silver carbonate method. × 300.

By the gold-sublimate method the cytoplasm both of the cell-body and its processes is seen to contain numerous small vacuoles. By the uranoformol and tannic-silver methods one sees, not vacuoles, but heavily impregnated granules to which Fieandt gave the name of gliosomes. They vary from oval or elliptical forms to bacillary rods, and seem to be in large part of the nature of mitochondria, as Nageotte first supposed. Other granules are occasionally found, sometimes forming wart-like excrescences on the larger processes. Pigment, large lipoidal masses, vacuoles, and many other inclusions have been described in these cells by Alzheimer and others.

The centrosome is usually a rather heavy granule, surrounded by a clear halo, and lying at the base of the largest process, often the sucker process. Its presence enables one to distinguish at a glance a neuroglial cell from the neurones and from the other interstitial cells. A reticular apparatus of Golgi can be demonstrated in the protoplasmic astrocytes of lower animals, but has not been found in the adult human.

Held, Fieandt, and Hardesty all speak of a syncytium formed by these cells, but this cannot be demonstrated by the methods of Golgi or Cox, by which definitely isolated branching elements are impregnated. Hence if a syncytium actually exists in the central nervous system it certainly is not formed by the neuroglia.

Probably every cell has one or more of the large processes, which end in an expansion or foot on the wall of a small blood-vessel; and many of the other cellular processes entwine themselves around the cell-body or the principal dendrites of the neurones. No fibrils of Ranvier-Weigert are present, although they may develop under pathological conditions.

Twin cells which appear to have recently divided are often found with flat surfaces adjacent to each other, with the centrosomes at opposite poles, and it is important to recognize this power of adult protoplasmic cells to divide amitotically.

Fibrillary Astrocytes.—There are two types: small cells with few processes and large ones with many. The distinguishing feature of both types is the presence of fibrils of Ranvier (Fig. 10, b), which develop in the cytoplasm of the stoutest process, often that with the " sucker foot," and gradually invade the entire cell. Contrary to Weigert's view they remain, at least in part of their extent, enveloped in protoplasm. The perivascular " sucker feet " are also a distinguishing characteristic of these cells, and it is interesting to note that they have no gliosomes, nor do they possess a Golgi reticular apparatus. The centrosome is a single heavy granule, usually at the base of the sucker process.

Oligodendroglia.—There has been as yet no thorough study of the development of the *oligodendroglia,* but fragmentary observations by Hortega [36] indicate that these cells originate from indifferent cells which wander among the fibres of the long nervous pathways and there differentiate into oligodendroglia, and also occasionally into fibrillary neuroglial cells. They are therefore of ectodermal origin and akin to the protoplasmic and fibrillary astrocytes. The oligodendroglial cells (Fig. 10, c), which are small compared to the other interstitial cells, have spherical nuclei with a heavy chromatinic network. The size of their nuclei is intermediate between that of the microglial and neuroglial nuclei. Their cytoplasm is unstained by ordinary methods (Fig. 11), including Nissl's methylene blue. By the uranoformol method it appears homogeneous. Hortega's silver carbonate reveals, in many cases, a spongy or reticulated structure. There are small granules analogous to gliosomes, a rudimentary reticular apparatus, and a diplosome which is very difficult to stain. The processes are slender, rarely branch dichotomously, have no lateral excrescences, but show at irregular intervals small enlargements, in the centre of which appears a vacuole by Hortega's method and a granule by Robertson's (Fig. 12). There are no fibrillæ of Ranvier, although the processes may sometimes appear fibrous, due to condensation of the protoplasm by reagents. These cells are found, for the most part, in long rows among the fibre tracts of the centrum ovale, bulb, protuberance, and spinal cord. In the gray matter they are almost exclusively satellites, preferring the bases of the neurones. Sometimes they are found in the angle of branching capillaries.

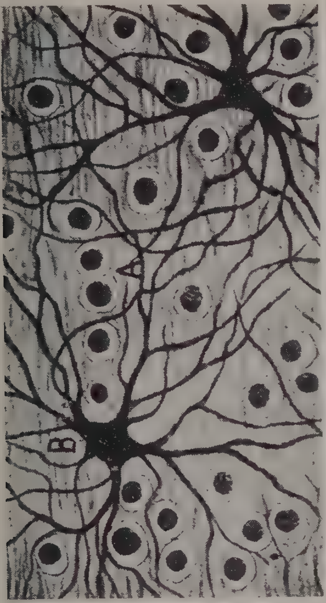


Fig. 11.—Oligodendroglia and fibrillary astrocytes. Human. Gold-sublimate method. (After Hortega.) a, oligodendroglia. b, fibrillary astrocytes.

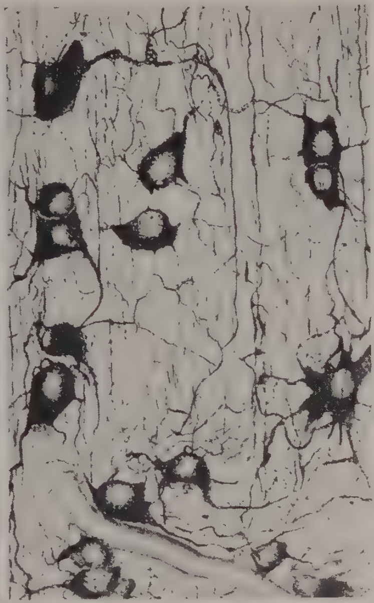


Fig. 12.—Oligodendroglia in cerebellar white matter of cat. Hortega's method. (After Penfield.)

The Microglia.—There are no studies of the development of the microglia in the human being, but Hortega's observations [35] on lower animals indicate that they are of mesodermal origin and spread from the pia mater and the choroidal telas into the central nervous system rather late in its development. The microglial cells (Fig. 10, d), though scattered throughout the brain substance, predominate in the gray matter. The nucleus, which is smaller than the nuclei of the other interstitial elements, is ovoid or elongated, and possesses a very heavy chromatinic network. The cytoplasm is especially scanty, and arising almost from the nucleus are two, three, or sometimes more processes, each of which divides dichotomously, often two or three times. The processes are covered with spiny excrescences coming off at right angles, by which they can be easily distinguished from the neuroglial cells. Occasionally granules of lipoid or pigment may be found, but there are no gliosomes, no glia fibrillæ, no reticular apparatus, and no centrosome.

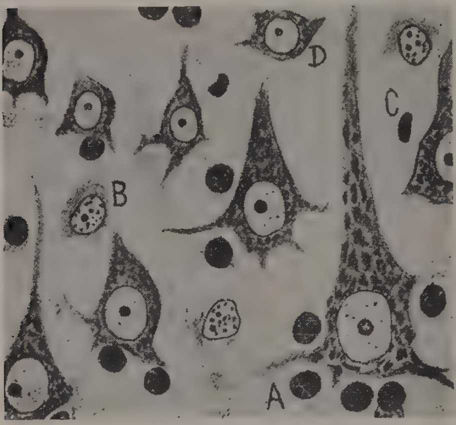


Fig. 13.—Normal human cerebral cortex showing character of nuclei of different cells. Nissl's method. (After Hortega.) a, Oligodendroglia. b, Neuroglia. c, Microglia. d, Neurone.

The cells, which are migratory elements, abound in the gray matter of the cerebrum, cerebellum, and spinal cord, where they lie free or are found as satellites of the neurones and blood-vessels.

In the normal brain these four adult elements which have thus far been discussed (the neuroglial, microglial, oligodendroglial, and nervous cells) may be distinguished with a certain degree of accuracy merely by their nuclei (Fig. 13), but a study of their processes in the manner described is essential for precise differentiation. In addition, one must consider three types of cells which have undergone a special development—the pineal, choroidal, and ependymal cells.

Pineal Cells.—In one restricted area of the roof-plate, the cells of the medullary epithelium proliferate to form the pineal proparenchyma, which in addition to neuroglial cells contains also the parenchymatous cells of the pineal body—a unique type of cell (Fig. 14, a) characterized, as Hortega [34] has shown, by a huge spherical nucleus, numerous blepharoplasten (Fig. 14, b), and thick processes ending in bulbs.

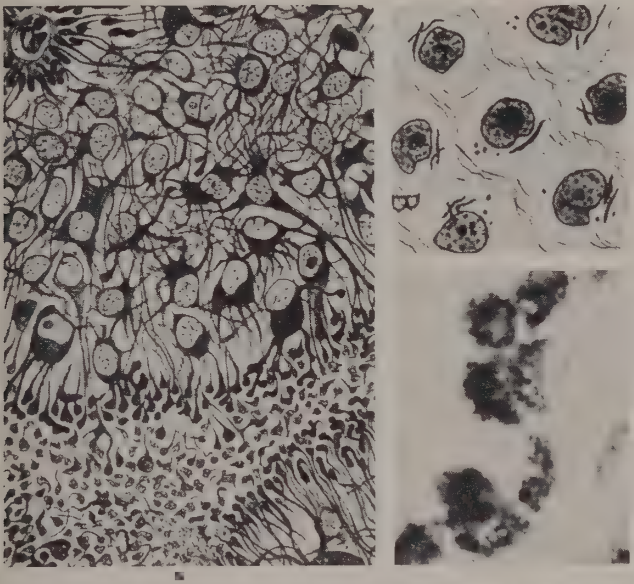


Fig. 14.—a, Cells of the pineal parenchyma. Human adult. Hortega's method. (After Hortega.) b, Blepharoplasten in cells of the pineal parenchyma. (After Hortega.) c, Choroidal epithelium. Human. (After Davis.) Shows numerous mitochondria.

Choroidal Cells.—In the region of the chroidal telas the primitive epithelium transforms itself directly into the cuboidal epithelium which covers the choroidal tufts. These cells are ciliated for a long time during fœtal life, but soon lose their cilia, together with the blepharoplasten which lie at their base. Their cytoplasm becomes packed with coarse granules (Fig. 14, c), most probably mitochondria, as originally pointed out by Ciaccio [12] and recently confirmed by Davis [14] from this clinic.

THE EPENDYMAL CELLS.—As stated, the cell-bodies of some of the primitive spongioblasts remain attached along the ventricular wall. They lose their cilia, except in a few restricted areas such as in the median raphe of the fourth ventricle (Fig. 15), and the blepharoplasten collect in a group in the cytoplasm, in which state they might be called *ependymal* spongioblasts. But should they also lose their peripheral processes they are reduced to the cuboidal cells lining the cerebral ventricles and central canal of the spinal cord, known as the *ependyma,* in which blepharoplasten can still be identified (Fig. 16).

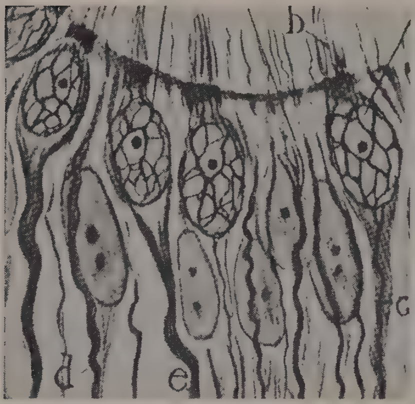


FIG. 15.—Ependymal cells of cat at one and one-half months. Pyridine-silver method. (After Cajal.) When these cells lose their cilia and the blepharoplasten collect in the cytoplasm as in Fig. 16, they are called ependymal spongioblasts.

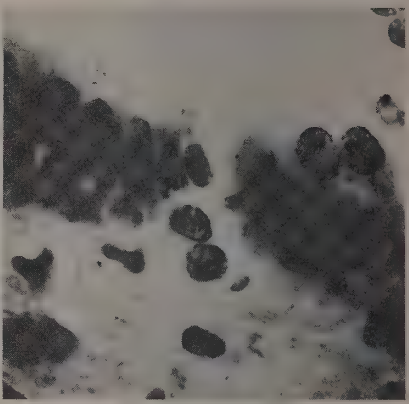
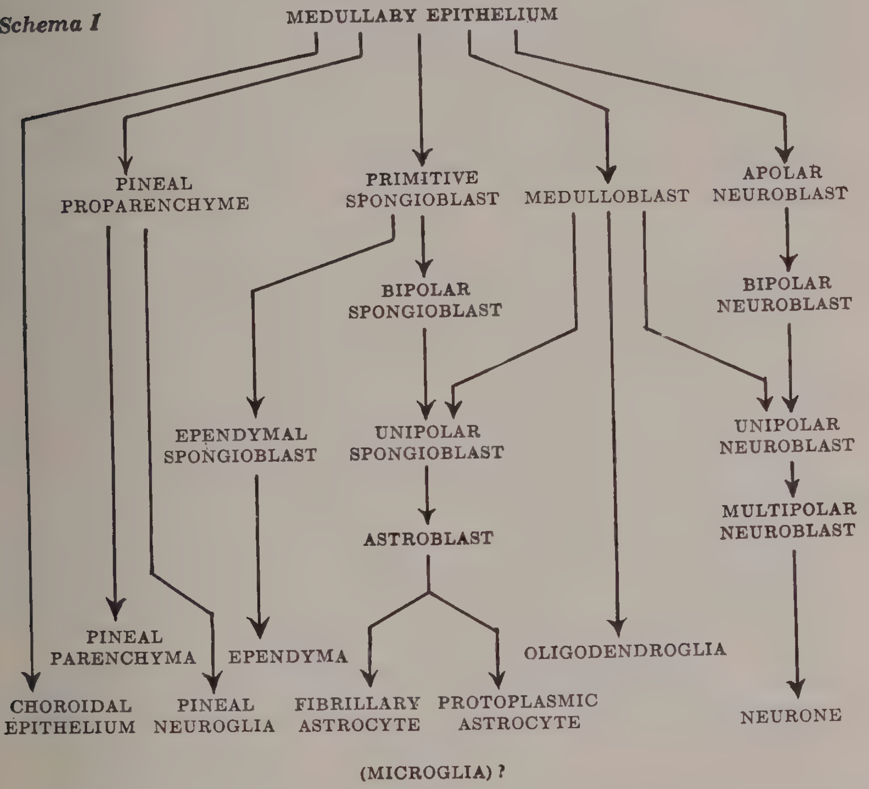


FIG. 16.—Blepharoplasten in ependymal cells of lateral cerebral ventricle. Hortega's fourth variant.

The foregoing brief account of the histogenesis of the brain may be represented in the accompanying diagram (Schema I).

Schema I



Since reference will be made later on to the analogies existing between the tumors of the retina, or the sympathetic nervous system, and those of the brain, it may be proper to include here a brief account of the histogenesis of the cells of these parts of the nervous system, together with a corresponding schema appropriate to each of them.

HISTOGENESIS OF THE RETINA

The cells of the retina bud off from the medullary epithelium. Those which maintain their attachment to what was originally the ventricular surface may transform themselves either into the rods and cones, into the cells of Müller (Fig. 17), into the pigment epithelium, or into the cylindrical cells of the pars ciliaris; but others leave the surface and proliferate as undifferentiated cells, which may be called *retinoblasts.* They become, according to Cajal,[8] the neuroglial cells of the fibre layer, the amacrine cells, and the nerve cells of the horizontal, the bipolar, and the ganglionic layers.

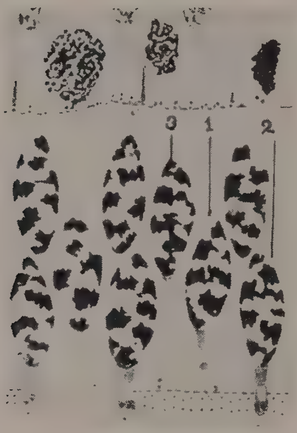


Fig. 17.—Retina of thirty-six hour cat. Iron hematoxylin stain. (After Leboucq.) 1, rods. 2, cones. 3, Müller's cells.

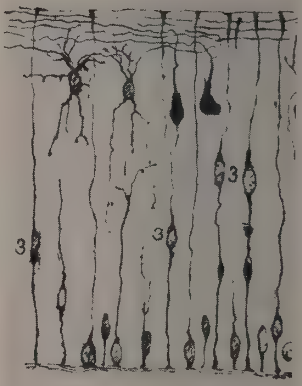
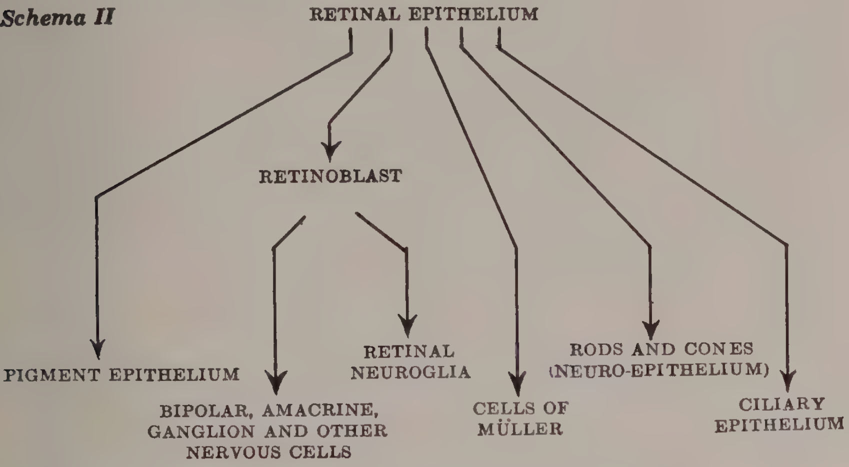


Fig. 18.—Retina of mouse at term. Golgi's method. (After Cajal.) 3, Müller's cells.

The rods and cones, since Schwalbe's description of them, are often known as the neuro-epithelium, for they constitute a sensory epithelium, and are as analogous to ependymal cells as they are to neurones. The development of the retina may be represented in Schema II.

Schema II



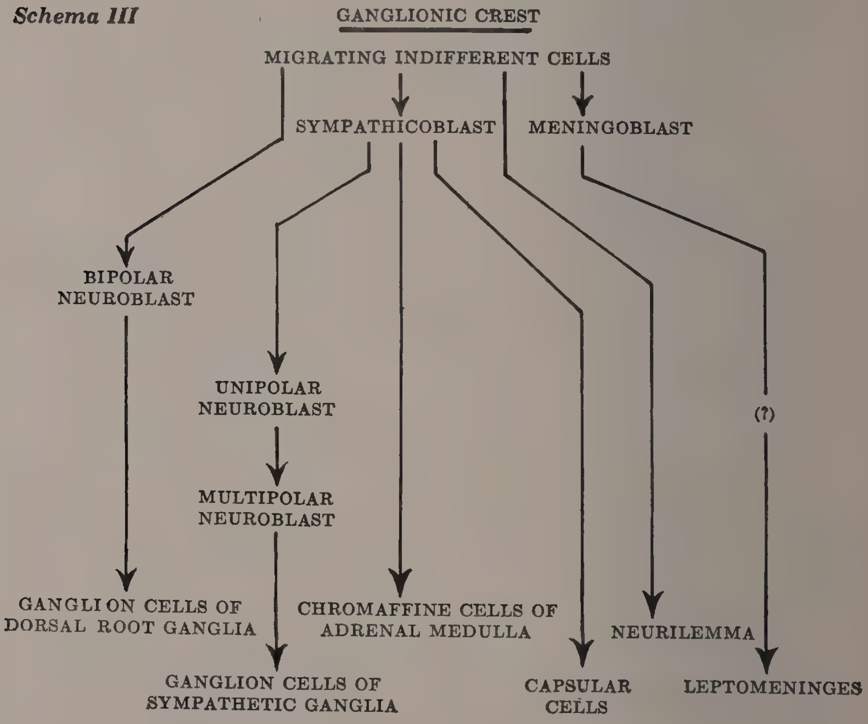
HISTOGENESIS OF THE SYMPATHETIC NERVOUS SYSTEM

The cells of the ganglionic crest undergo a developmental change somewhat comparable to that of the medullary epithelium (Harrison [28]). They migrate ventrally from their original position along the dorsal surface of the medullary tube. A group collects in each metamere and becomes the anlage of the dorsal root ganglion. Some of the cells in each metameric group then differentiate into the familiar bipolar neuroblasts which form the dorsal roots of the spinal and analogous cranial nerves. Others become the capsular cells which surround the adult neurones.

Meanwhile other cells of the ganglionic crest migrate along the motor nerves to become the sheath cells of Schwann or *neurilemma,* and a few cells also from the spinal cord appear to participate in the formation of this structure. Still other groups of cells, known as *sympathicoblasts,* migrate into the visceral areas to form the anlage of the sympathetic nervous system. When they reach their final stations they differentiate into the neurones of the sympathetic ganglia, the capsular cells of these ganglia, and into the *chromaffine* cells of the adrenal medulla and analogous structures.

Evidence is accumulating from embryological,[49] pathological,[50] and experimental [29] studies that the *meningoblasts* which form the leptomeninges are also migratory cells from the ganglionic crest. These differentiations may be represented in diagramatic form in Schema III.

Schema III



C. HISTOLOGICAL METHODS

For the purposes of this study the abundant pathological material at hand has been thoroughly reinvestigated, and the attempt has been made to recognize the various cellular types discussed in the preceding section. In order to do so methods were employed which include perhaps all the important ones except that of Golgi, which is unsuited for our purposes as too capricious. The material collected before this study was undertaken consists of tissues preserved for the most part in 10 per cent. formalin and a number of surgically removed specimens in 80 per cent. alcohol after primary fixation in Zenker's fluid. It has been found possible to utilize this valuable material in our study by the use of proper mordants. In the case of fresh material, however, after a long experience with trial and error, the following procedure has been adopted.

If only a small amount of tissue happens to have been removed at operation it is immediately fixed in 10 per cent. neutral formalin, for after this fixation the greatest number of histological methods may be employed. Frozen sections are cut first from the block of tissue, and the remainder is embedded in paraffin for further study. If sufficient tissue is available fragments are put in formalin-bromide, in Zenker's fluid, in pyridine, in ammoniated alcohol, etc. But the three best routine fixatives are 10 per cent. neutral formalin, formalin-bromide, and Zenker's fluid.

Should the brain be removed at necropsy it is previously injected with 10 per cent. formalin through the carotid arteries and fixed *in situ*. In the vast majority of cases this was done not later than six hours post mortem. It is fortunate that most of the older material at hand has been preserved in this way, since after formalin fixation the most comprehensive examination can be made, and the following staining or impregnation methods employed:

1. Ten per cent. formalin.
   a. On frozen sections:
      - Hortega's 1st variant for nuclei and neuroglial fibrillæ.
      - Hortega's 4th variant for protoplasmic neuroglia.
      - Perdrau's method for the connective tissue.
      - Spielmeyer's method for myelin sheaths.
      - Cajal's method for unmyelinated nerve fibres.
      - Bielschowsky's method for myelinated nerve fibres.
      - Herxheimer's method for fat.

   b. On paraffin sections:
      - Hematoxylin and eosin for nuclei.
      - Pötter's method for neuroglial fibrillæ.
      - Perdrau's method for connective tissue.
      - Loyez's method for myelin.
      - Bielschowsky's method for nerve fibres.
      - Bielschowsky-Plein for Nissl substance.

   c. On celloidin sections:
      - Weigert-van Giesen for *Übersichtsbilder*.
2. Formalin-bromide.
   - Hortega's method for the oligodendroglia.
   - Hortega's method for the microglia.
   - Cajal's gold-sublimate method for the neuroglia.
3. Zenker's fluid.
   - Mallory's phosphotungstic acid-hematoxylin method for neuroglial fibrillæ.
   - Bailey's method for neuroglial fibrillæ.
   - Methylene blue eosin for nuclei.

4. Pyridine.
    Held-Cajal method for early stages of neurogenesis.
5. Ammoniated alcohol.
    Ranson's method for unmyelinated nerve fibres.
    Cajal's reduced-silver method for neurofibrillæ.

The details of these methods are easily available * with the exception of that of Cajal[7] for unmyelinated nerve fibres on formalin-fixed tissue, which may be given briefly in view of the comparative inaccessibility of the original description to American readers.

1. Fix in 10 per cent. formalin 14 days or more.
2. Frozen sections, 15–20 mikrons.
3. Receive and conserve sections in same formalin sol. Wash rapidly in aq. dest. (2 changes).
4. Pass immediately into:
    Two per cent. nitrate of silver sol., 10 ccm.
    Pyridine (pure), 5–6 drops.
5. Leave 12 hours (not longer) in this silver solution in dark, until color of tobacco, and then place in 96 per cent. alcohol for one minute.
6. Without washing put them in the following reducer:
    Pure hydroquinone, 0.20 grams.
    Merck's formalin (not neutralized), 30 ccm.
    Aq. dest., 70–80 ccm.
7. Wash. Abs. alc. Clear. Mount in balsam.

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* Pathological Technique, Mallory and Wright, 1924, 8th Ed.; Microtomist's Vade Mecum, Lee, 1921, 8th Ed.; Les Techniques Anatomo-pathologiques du Système nerveux, Roussy-Lhermitte, 1914; Technik der mikroskopischen Untersuchung der Nervensystems, Spielmeyer, 1914, 2nd Ed.; Interstitial Tissues of the Central Nervous System, Bailey and Hiller, *J. Nerv. and Ment. Dis.*, 1924, LIX, 337; Oligodendroglia and its Relation to Classical Neuroglia, Penfield, *Brain,* 1924, XLVII, 430.

D. OCCURRENCE OF HISTOGENETIC CELLULAR TYPES IN BRAIN TUMORS

By the histological methods just described it has been possible to identify in our series of brain tumors practically every cellular type described in the section which deals with the histogenesis of the brain. A short account will now be given of the frequency of occurrence and distribution of these various types, accompanied by a series of photomicrographs which may be compared with the illustrations already used to clarify the discussion of their origin in the nervous system. It may be helpful to reënumerate the cell types, and to consider them in turn :

TABLE I. ENUMERATION OF CELL TYPES.

1. Medullary epithelium.
2. Medulloblast (indifferent cells of Schaper).
3. Pineal proparenchyma.
4. Pineal parenchyma.
5. Primitive spongioblast.
6. Ependymal spongioblast.
7. Ependyma.
8. Bipolar spongioblast.
9. Unipolar spongioblast.
10. Astroblast.
11. Protoplasmic astrocyte.
12. Fibrillary astrocyte.
13. Oligodendroglia.
14. Apolar neuroblast.
15. Bipolar neuroblast.
16. Unipolar neuroblast.
17. Multipolar neuroblast.
18. Neurone.
19. Microglia.
20. Choroidal epithelium.

1. Medullary Epithelium.—In Figure 19 are shown two photographs of a tumor which grew from the postinfundibular

recess of the floor of the third ventricle. It will be seen from "a" that the tumor tends to grow in bands of cells having a striking resemblance to the medullary plate. These bands of cells fold themselves, here and there, to form a sort of medullary tube, and in places they have a definite internal and external limiting membrane (Fig. 19, b). In only one other tumor were similar cells found—a tumor which apparently had its origin in the region of the pineal body.

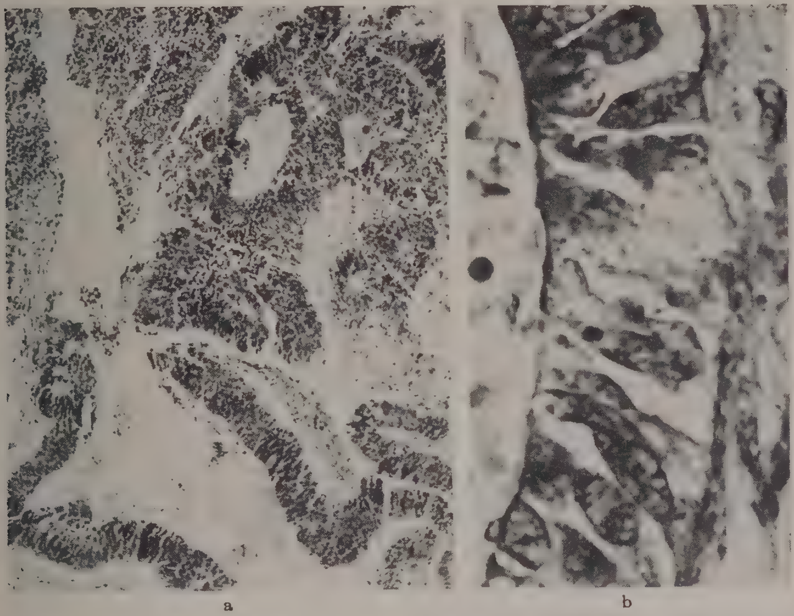


FIG. 19.—Neoplasm reproducing the structure of the medullary epithelium. a, Surg. No. 17041. Methylene blue-eosin stain. × 80. Cells growing in long bands, folded in places to form canals. b, Idem. Phosphotungstic acid-hematoxylin stain. × 850. To show the external and internal limiting membranes of the bands of cells.

Where the cells within the tumor are so arranged as to make canals, one may see in sections stained by phosphotungstic acid-hematoxylin the formation of a membrane just outside of the inner extremities of the cells (Fig. 20), resembling the internal limiting membrane of the retina, or the similar membrane described by Verhoeff[71] in the pigment layer. These cells bear neither cilia nor blepharoplasten. Many years ago it was pointed out by Benda[21] that one could expect tumors with such characteristics to develop only from certain regions of the roof- or floor-plate, or from the pars ciliaris retinæ, for only in these regions does the medullary epithelium persist in an undifferentiated form.

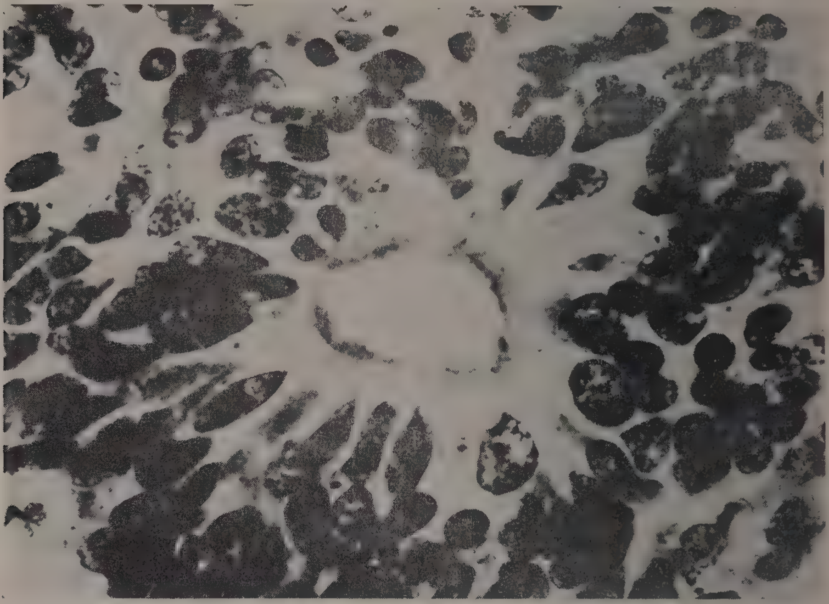


Fig. 20.—Detail from the tumor shown in Fig. 19. Note the membrane forming just outside of the inner extremities of the cells. Surg. No. 17041. Phosphotungstic acid-hematoxylin stain. × 850.

2. Medulloblast.—Many tumors of the brain consist almost wholly of small cells with round or slightly oval nuclei and scanty cytoplasm. That these cells represent the indifferent cells of Schaper (medulloblasts) may be inferred from the fact that occasionally among them will be found both spongioblasts and neuroblasts, as will be described in detail in a later section

(p. 59). The cells are usually shaped somewhat like a carrot, and the nuclei have a tendency to arrange themselves around clear spaces filled with the longer poles of the cells (*cf.* Fig. 21).

3. Pineal Proparenchyma.—It has been related how the cells of the roof-plate, in the region of the recessus pinealis, proliferate to form the anlage of the pineal body. At first these cells are undifferentiated, consisting simply of a spherical nucleus surrounded by a scanty ring of cytoplasm. Tumors found in this region are sometimes composed of a mass of such undifferentiated cells. The similarity of their structure to that of the pineal anlage may be appreciated by comparing " a " and " b " in Figure 22, borrowed from the paper of Horrax and Bailey,[33] which deals with this subject. These tumors were there described under

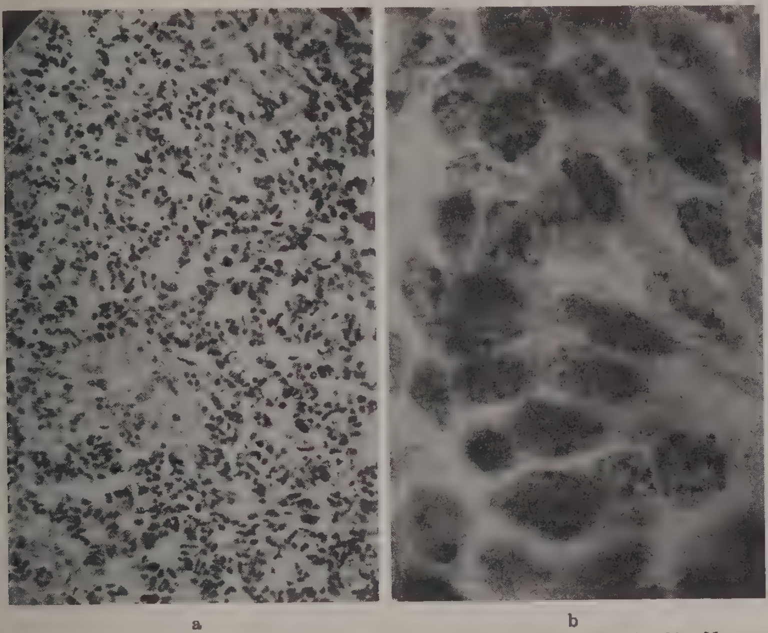


Fig. 21.—Medulloblasts. a, Surg. No. 367. Hematoxylin and eosin stain. × 100. Numerous pseudorosettes. b, Idem. × 1000. Carrot-shaped cells are seen.

the name of spongioblastoma pinealis, since they consist of cells analogous to the proparenchyma of the pineal body.

4. Pineal Parenchyma.—Adult cells of the pineal parenchyma are rarely seen. The cells which chiefly compose the pinealomas are large spheroidal cells with huge vesicular nuclei.

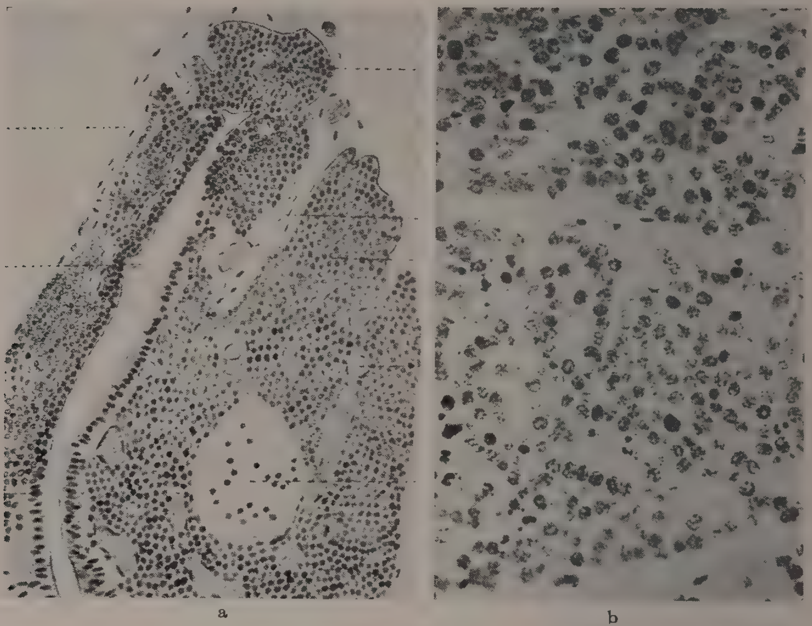


Fig. 22.—a, Anlage of human pineal body at fifth foetal month. (After Krabbe.) b, Pineoblastoma. Note resemblance to pineal anlage in "a". Surg. No. 5627. Neutral ethyl violet-orange G. stain. × 300.

Their cytoplasm contains mitochondria in abundance and occasionally other granules (Fig. 23, a), probably to be interpreted as blepharoplasts, are to be seen. The cells have for the most part short, stubby processes, but longer ones ending in end-bulbs may be encountered (Fig. 23, b).

5. Primitive Spongioblasts.—Most of the pseudo-epithelial formations seen in brain tumors probably are composed of these cells. They surround small canals or cavities, and are

characterized by a columnar body lying between the nucleus and the cavity, whereas a long tail extends away in the opposite direction, there being no basement membrane as in a true epithelium.

The columnar bodies of these cells lining the canals are covered by a cuticular membrane bearing minute blepharoplasten.

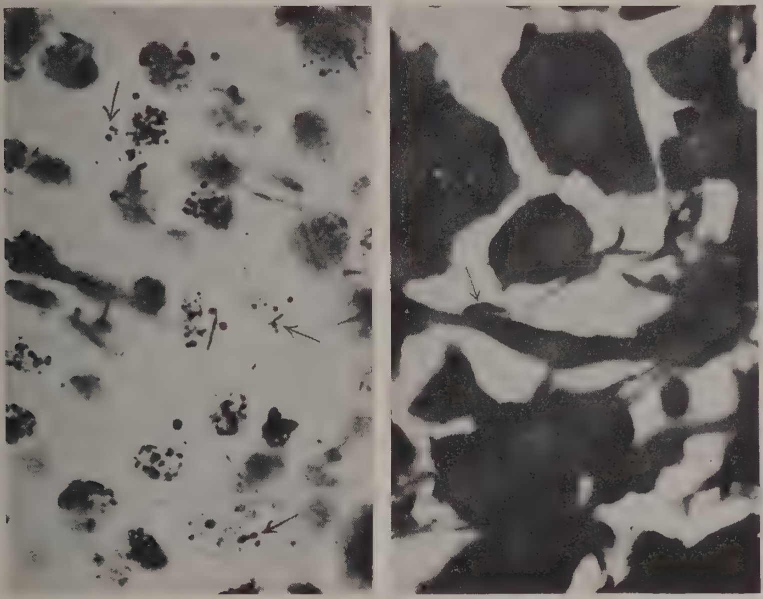


FIG. 23.—Parenchymal cells from a pineal tumor. a. Surg. No. 21099. Hortega's fourth variant. × 850. Blepharoplasten are seen in the cells (arrows). b, Idem. Walter's gold chloride method. × 850. End-bulb indicated by arrow.

In some cases cilia have been seen, but in the example here reproduced (Fig. 24, b) no cilia are seen, although there is some granular material on the inner surface of the cuticular membrane which may represent the remains of cilia, the necropsy in this particular case having been performed many hours post mortem. The tails of the cells are very difficult to demonstrate, for they give the reactions neither of neuroglial fibrillæ nor of nerve fibres. Rosenthal succeeded in impregnating the cells in their entirety by means of Golgi's method, and his illustrations show typical primitive spongioblasts (compare Figures 2 and 24, a).

Such primitive spongioblasts are sufficiently rare in brain tumors to excite considerable interest. They are more commonly seen in tumors of the spinal cord, and are often found in gliomas of the retina, where they surround small cavities to form what were described by Flexner [20] as rosettes. He supposed them to be analogous to the rods and cones, the so-called neuro-epithelium of the retina. Mawas,[45] who also shares this belief, has pointed out that each cell bears a single cilium with a diplosome at its base, whereas the primitive spongioblasts of

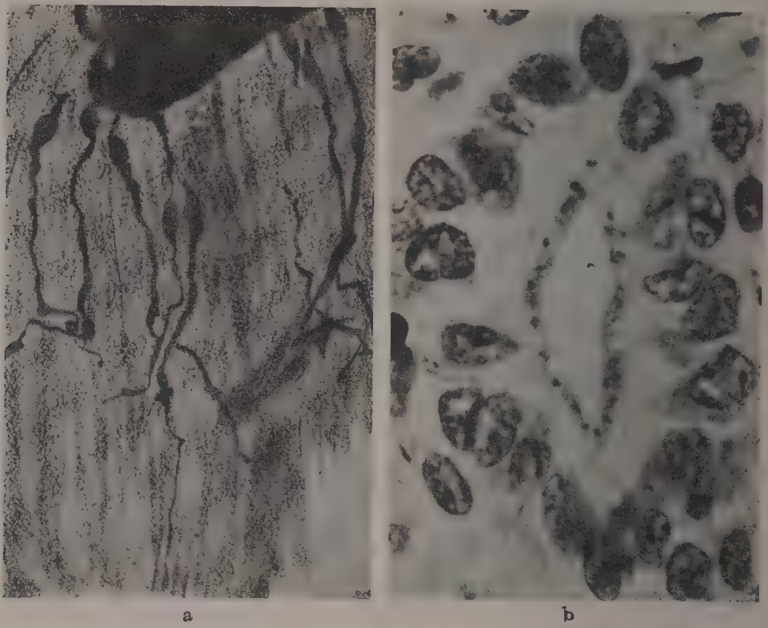


FIG. 24.—a, Primitive spongioblasts from a tumor of the spinal cord. Golgi's method. After Rosenthal.) b, Primitive spongioblasts in brain tumor. Surg. No. 15265. Neutral ethyl violet-orange G. stain. × 850. Blepharoplasten in central ends of the cells.

the developing brain bear several cilia with numerous diplosomes. This, however, is an insufficient distinction, since many primitive spongioblasts in the olfactory bulb have a single diplosome, and as Leboucq[37] points out, so have the cells of Müller in the retina. Verhoeff[71] in turn has made clear that the central ends of the cells of the rosettes may project beyond the limiting membrane (Fig. 25, a), a sufficient evidence, therefore, that some of these cells are embryonic rods and cones. The remainder may just as well represent the embryonic cells of Müller, and the distinction is of slight importance since, as already pointed out in the section on histogenesis, the rods and cones are more analogous to ependymal cells than to nerve cells.

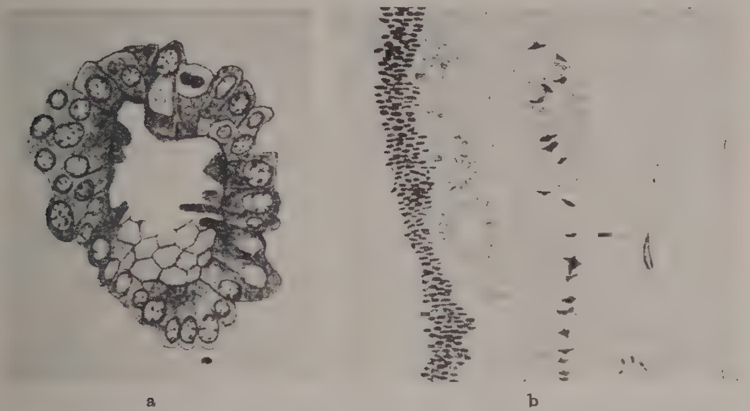


Fig. 25.—a, Rosette from a retinal glioma. Phosphotungstic acid-hematoxylin stain. (After Verhoeff.) Inner ends of cells project beyond the limiting membrane after the manner of rods and cones. b, Malformation formed of medullary epithelial cells. Human retina. (After Ginsberg.)

Many similar formations in other tumors have come to be called "rosettes," although it would be preferable to restrict this term to small canals surrounded by primitive spongioblasts (Fig. 26, a), whether in tumors of the retina, brain, or spinal cord. The most familiar of the pseudo-rosettes are the ball-like groups of cells which occur (Fig. 26, b) in sympathicoblastomata (neuroblastoma). They differ from true rosettes in having no central cavity, the centre of the "ball" being filled with the tails of the cells. They were properly interpreted by Ribbert[59] in describing a tumor of the third ventricle.

Formations simulating rosettes may also be found in tumors of the roof- or floor-plate of the brain (Fig. 20), of the pars ciliaris retinæ, or in malformations of the retina (Fig. 25, b). They differ from true rosettes in that the epithelial cells have a basement membrane, and their central ends bear neither cilia nor blepharoplasten. Degeneration may sometimes also give rise to pseudo-rosettes (Fig. 27, a), the central cavity being due to necrosis. Furthermore, the radiation of cells around blood-vessels also may at times give a rosette-like appearance (Figs. 27, b and 45, a).

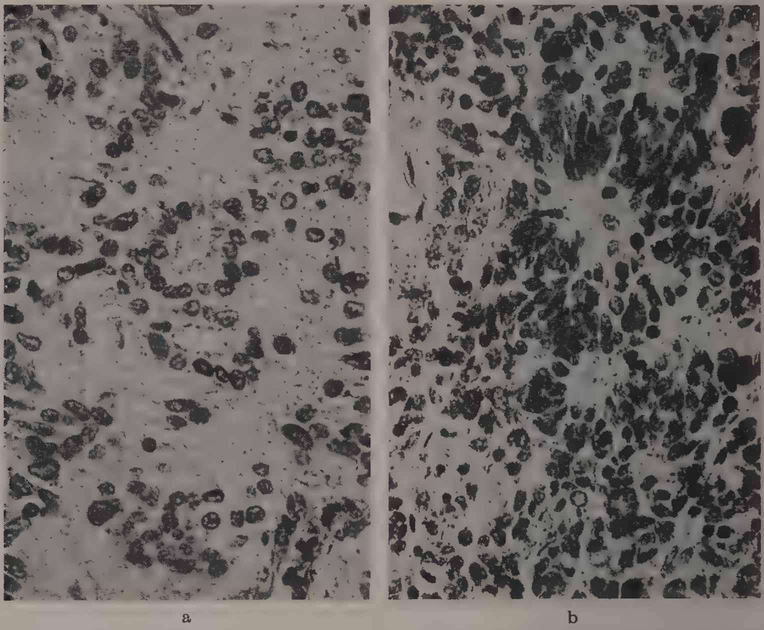


FIG. 26.—a, Surg. No. 15265. True rosettes from a brain tumor. Neutral ethyl violet-orange G. stain. × 300. b, Surg. No. 367. Pseudo rosettes. Ball-like arrangement of cells in a medulloblastoma. Phosphotungstic acid-hematoxylin stain. × 300.

6. Ependymal Spongioblasts.—The ependymal spongioblast differs from the primitive spongioblast in the absence of cilia, in the collection of blepharoplasten in the cytoplasm near the nucleus, in its more coarsely granular and abundant cytoplasm, and in its heavier tail, which stains with methods for demonstrating neuroglial fibrillæ, and shows a tendency to radiate toward blood-vessels.

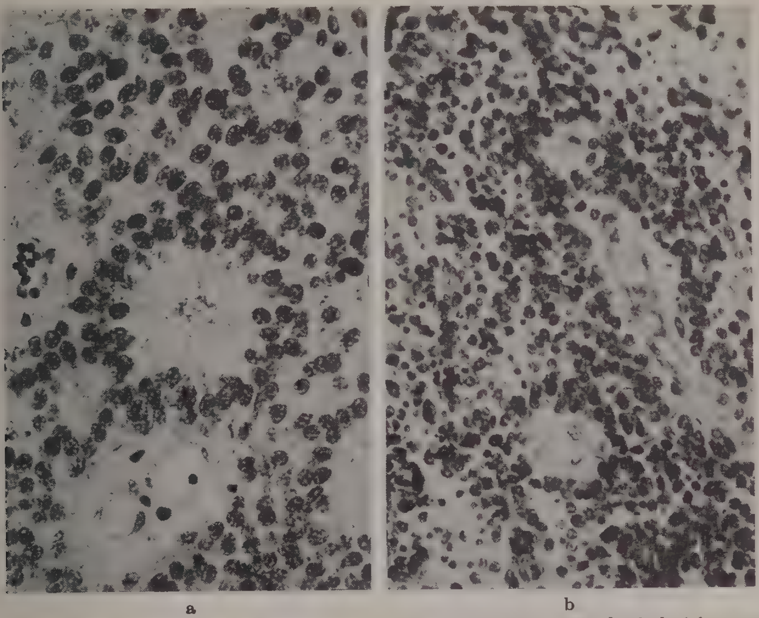


Fig. 27.—a, Pseudo-rosette due to degeneration. Surg. No. 18049. Neutral ethyl violet-orange G. stain. × 300. b, Perivascular pseudo-rosette. Surg. No. 5611. Hematoxylin and eosin stain. × 300.

Ependymal spongioblasts may occur as isolated cells in many tumors, but certain growths commonly found in the region of the fourth ventricle may be almost entirely composed of them. Their appearance in such cases is shown in Figure 28, a, in which the cells can be seen to have arranged themselves like a pseudo-epithelium, with the tails streaming away from their inner ends, and with blepharoplasten clearly to be seen under a higher magnification (Fig. 28, b).

7. Ependyma.—Tumors composed of these cells are rare, and, like the above, occur usually in the fourth ventricle, but are also found in the lateral ventricles or central canal of the spinal cord. The cells are polygonal, with abundant cytoplasm and sharply defined boundaries. They are characterized by the presence of a group of from two to a dozen granular or short rod-shaped blepharoplasten which lie in a clear zone in the cytoplasm near the nucleus (Fig. 29). Occasionally such granules are seen in neuroglial cells near the ventricular surfaces, but they occur with great regularity only in the ependymal cells, and in the parenchymal cells of the pineal body. They must not

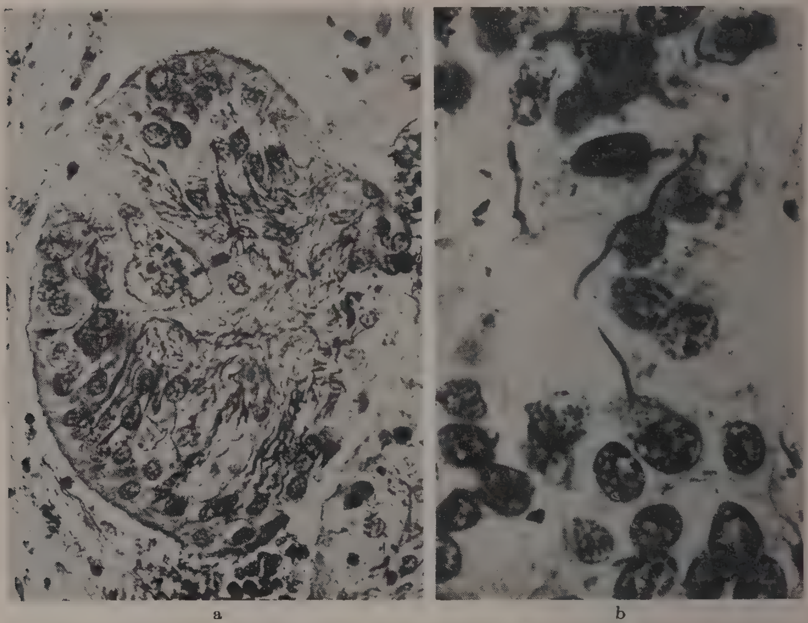


Fig. 28.—Ependymal spongioblasts from a cerebral neoplasm. a, Surg. No. 18049. Phosphotungstic acid-hematoxylin stain. × 300. The cells are arranged to form a pseudoepithelium. b, Detail from "a". Neutral ethyl violet-orange G. stain. × 850. Blepharoplasten are clearly seen in one cell.

be confused with the multiplication of centrosomes seen in giant cells, a phenomenon very commonly observed both in gliomas and sarcomas.

8. Bipolar Spongioblast.—Bipolar, spindle-shaped cells are exceedingly numerous in many brain tumors, and certain tumors of the type known as " gliosarcoma " are almost wholly composed of them (Fig. 30, a). The superficial resemblance to a spindle-celled sarcoma may be very striking, but on closer examination the cells are found to be less regular in outline, as shown in Stroebe's original drawing (Fig. 30, b). The ends of the cells are frayed, and since collagenic fibrils are never found, the delicate neuroglial fibrillæ, sometimes present, can hardly

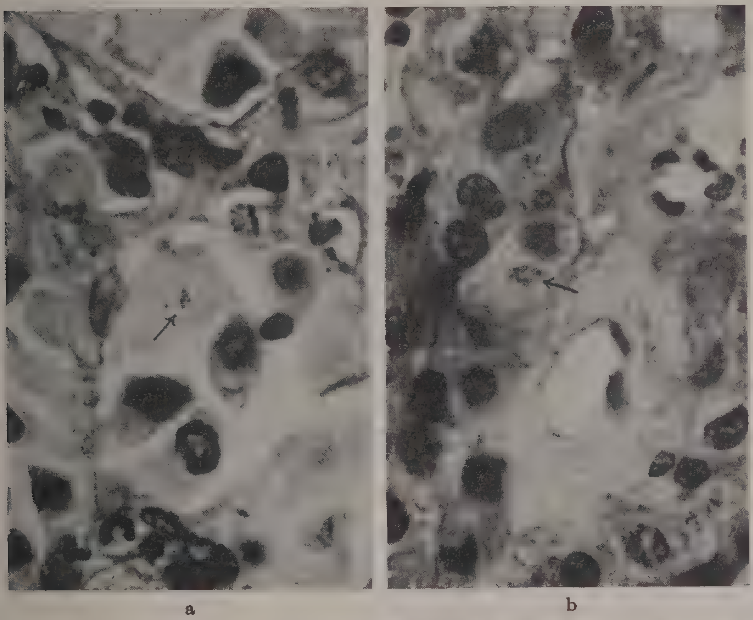


Fig. 29.—Ependymal cells from tumors. a, Surg. No. 357. Phosphotungstic acid-hematoxylin stain. × 850. Blepharoplasten in centrally situated cell. b, Surg. No. 17061. Neutral ethyl violet-orange G. stain. × 850. Numerous blepharoplasten in the cells.

be confused with fibroglial fibrillæ, although both stain with the same dyes.

Perhaps the best evidence of the spongioblastic nature of these cells is the fact that some of them become heavily impregnated by the gold-sublimate of Cajal, an occurrence never seen in a spindle-celled tumor of connective-tissue origin. Also the method of Cajal often reveals imperfectly developed astrocytes mingled with the spindle-shaped cells. Figure 30, a, shows the appearance of the latter when impregnated with Cajal's gold-sublimate. The whole structure is less compact than that of a spindle-celled sarcoma, and more nearly resembles that of an acoustic neurinoma, the cells of which are also of ectodermal origin.

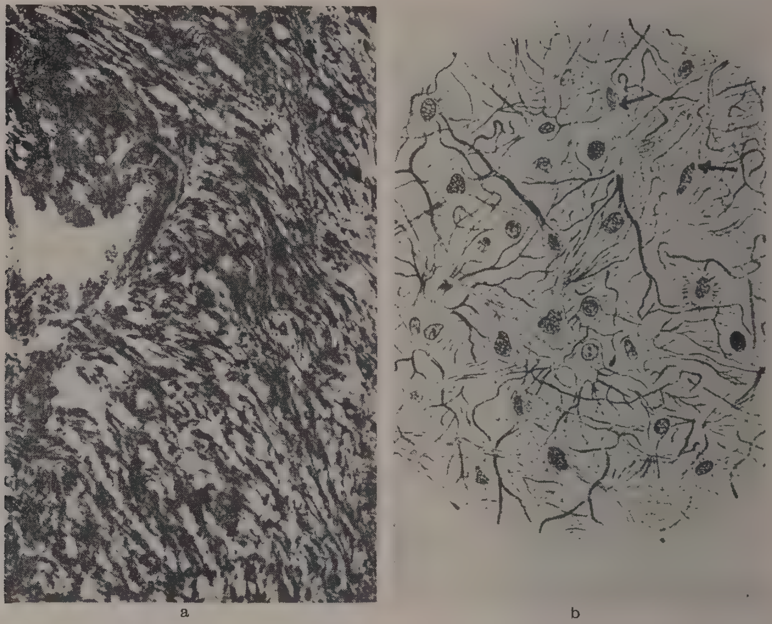


FIG. 30.—a, Bipolar cells from a brain tumor. Surg. No. 21093. Gold-sublimate method. × 300. b, Copied from Stroebe. Drawn from a mixed glioma of the pons. Several typical bipolar spongioblasts are shown (arrows).

9. Unipolar Spongioblasts.—These cells also are a common finding in brain tumors. They sometimes assume a palisade arrangement (*cf.* Fig. 62, b), but since a very similar formation is often due to necrosis the two should not be confused. In the latter, the areas free from nuclei are occupied by a necrotic mass; in the former the free area is occupied by the tails of the spongioblasts. A typical unipolar spongioblast from the edge of such an area is shown in Figure 31, c, and also in Figure 31 other cells are depicted, as seen by various staining methods. The essential characteristics are a piriform cellular body, having a single long process with a heavy centrosome at its base. Rarely whole tumors may be composed of such cells.

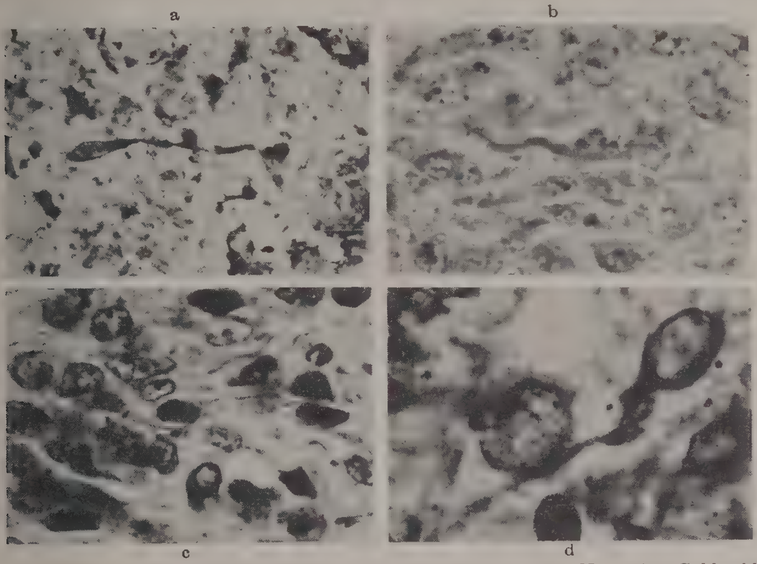


Fig. 31.—Showing unipolar spongioblasts by various methods. a, Surg. No. 18670. Gold-sublimate method. ×850. b, Surg. No. 11463. Neutral ethyl violet-orange G. ×850. c, Surg. No. 15581. Phosphotungstic acid-hematoxylin. ×850. d, Surg. No. 2527. Perdrau's method, modified. ×1000.

10. Astroblast.—Isolated cells of this type in different stages of development are frequently encountered in brain tumors, but occasionally almost an entire growth will be com-

posed of astroblasts alone. They are shown most clearly by the gold-sublimate method of Cajal (Fig. 32, a). Their vascular "sucker feet" (Fig. 32, b) are an unmistakable characteristic.

11. Protoplasmic Astrocytes.—Protoplasmic astrocytes occur in great numbers and many brain tumors, as will be seen, are composed entirely of them. They are not easily identified by the usual staining methods, though they may be (Fig. 33, a), whereas the gold-sublimate method of Cajal readily shows (Fig. 33, b) their long, thick processes. They occur almost always among cells of more embryonic type.

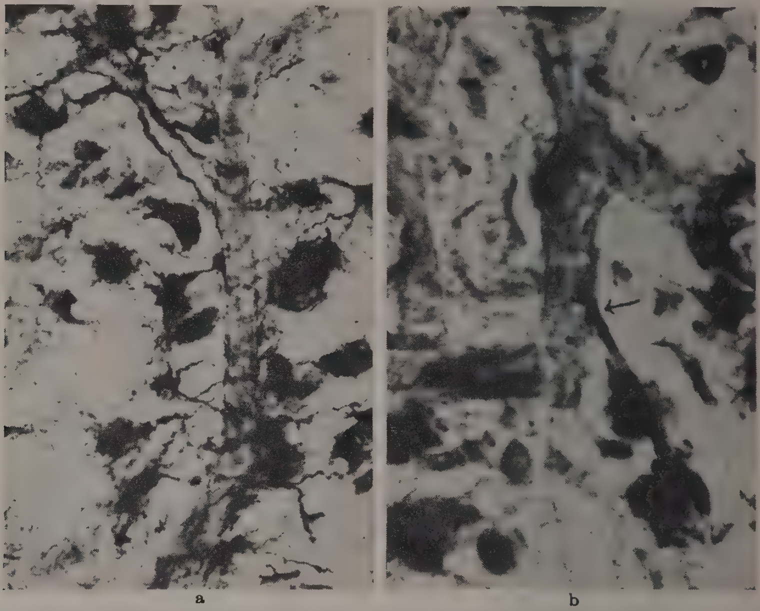


Fig. 32.—Astroblasts. a, Surg. No. 20487. Gold-sublimate method. × 300. Note the vigorous vascular feet and the feeble processes from the opposite poles of the cells. b, Surg. No. 6408. Phosphotungstic acid-hematoxylin stain. Cell in higher magnification, × 850, showing (arrow) vascular sucker foot.

12. Fibrillary Astrocytes.—These cells also are of common occurrence. In fact, it is the fibrillary astrocyte on which the diagnosis of glioma is usually made, for it produces the fibrillæ

which can be stained by the methods of Weigert, Mallory, Anglade, and others. It is also the cell with star-like radiations demonstrated by the older method of Golgi and the new gold-sublimate method of Cajal. Though it is usually found in combination with other more embryonic cells, tumors may be entirely composed of fibrillary astrocytes. Their appearance by two methods of impregnation is shown in Figure 34.

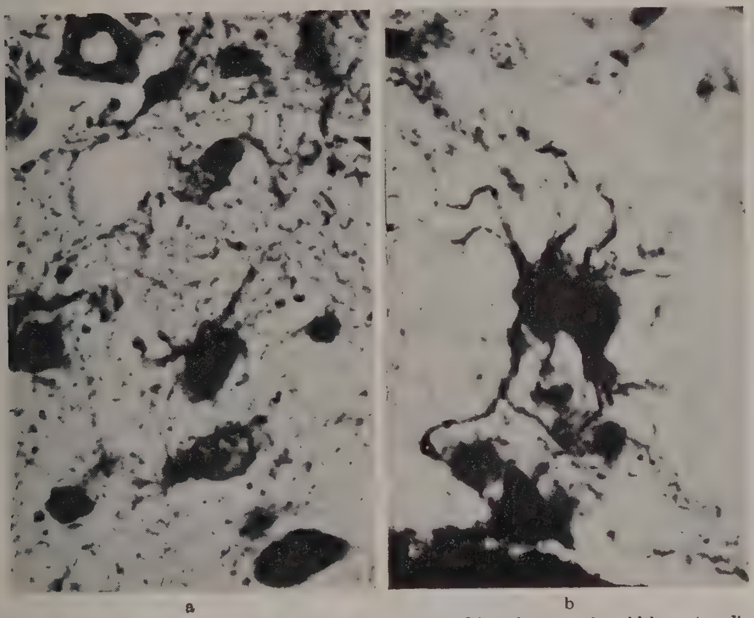


Fig. 33.—Protoplasmic astrocytes. a, Surg. No. 19042. Phosphotungstic acid-hematoxylin stain. × 850. Note the thick protoplasmic processes without fibrillæ. b, Surg. No. 19383. Gold-sublimate method. × 850.

13. Oligodendroglia.—Because of technical difficulties it has been impossible to obtain positive evidence of the presence of the oligodendroglia in our series of brain tumors. There is, however, much indirect evidence. Several tumors with histories of many years' duration have been found to be composed of small cells with round, heavily stained nuclei whose cytoplasm

has the peculiarity of taking a very feeble stain with the ordinary dyes. Moreover, an intercellular substance is present which is neither connective tissue, neuroglia nor nerve fibres, but consists of delicate protoplasmic extensions of the cells (Fig. 35, a). Occasionally among these cells poorly developed astrocytes will be shown by the gold-sublimate method (Fig. 35, b). It is most probable that the neoplastic cells are oligodendroglia. They are found scattered in many tumors, but their positive identification will necessarily await the routine use of some specific method such as that of Hortega or of Robertson.

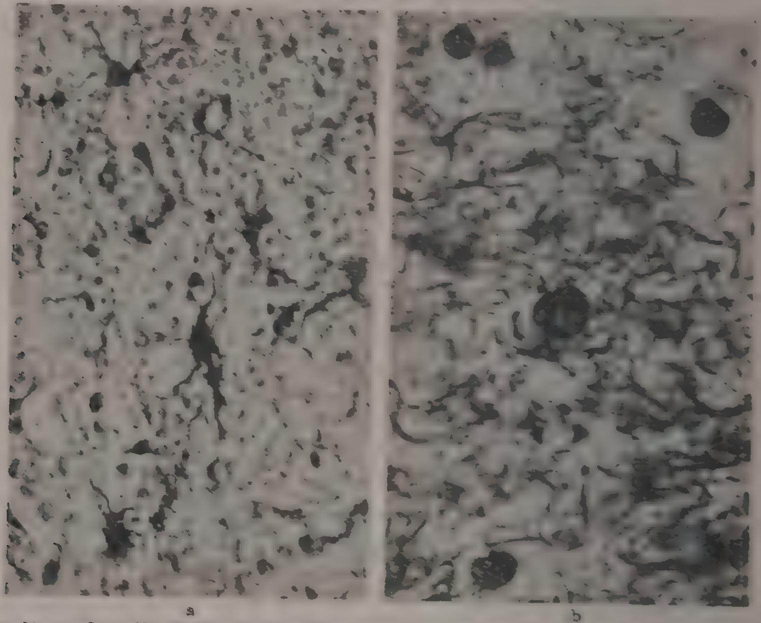


FIG. 34.—a, Surg. No. 20535. Gold-sublimate method. × 300. Isolated fibrillary astrocyte in an oligodendroglioma. b, Surg. No. 19099. Phosphotungstic acid-hematoxylin stain. × 550. Only the tangled fibrillæ of the astrocytes are seen.

14. APOLAR NEUROBLAST.—Neuroblasts of any kind are a rare finding in brain tumors. In a ganglioneuroma of the

medulla oblongata, Pick and Bielschowsky[54] observed many cells, possessed of large vesicular nuclei, but no processes which could be demonstrated. They interpreted them as apolar neuroblasts. There are in our series two tumors which seem to be composed almost wholly of such cells, though we have not ventured definitely to classify them. Inasmuch as, contrary to the usual opinion, we regard the neuroblastoma as a particularly rare tumor (*cf.* page 128), the pathological description of one of these two unaccepted examples may be briefly given:

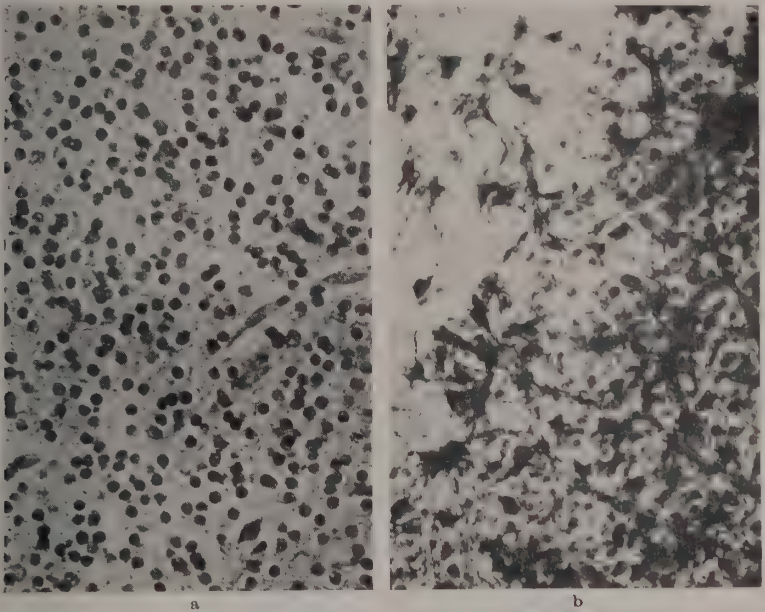


FIG. 35.—Tumors composed of oligodendroglia. a, Surg. No. 5490. Hematoxylin and eosin stain. × 300. Note the spherical, heavily stained nuclei, and clear halo surrounding each. b, Surg. No. 13185. Gold-sublimate method. × 300. Poorly developed astrocytes are impregnated.

A man 45 years of age entered the Johns Hopkins Hospital June 19, 1908 (Surg. No. 22551). He died after an exploratory craniotomy which disclosed a supposedly inoperable tumor. A complete necropsy showed no pathological change outside of the brain except a terminal pneumonia. In the brain, which had been fixed in 10 per cent. formalin before removal, was a large so-called glioma, 6 cm. in diameter, in the posterior portion of the left frontal lobe (Fig. 36).

On microscopic reëxamination the tumor is found to be fairly sharply circumscribed and everywhere separated from the meninges by a thin layer of cortical substance (Fig. 37). It is composed essentially of a loose mass of rounded or polygonal cells with abundant, coarsely granular cytoplasm, and a large spherical nucleus containing a heavy nucleolus and scanty chromatin network (Fig. 38, b). Mitotic figures are rare. In a few restricted areas were seen small cells resembling lymphocytes (Fig. 38, a) and all transitions from these to the larger cells composing the mass of the tumor. Stains for neuroglia revealed nothing. By Cajal's reduced-silver method a few bipolar cells (compare Fig. 39, a) were impregnated.

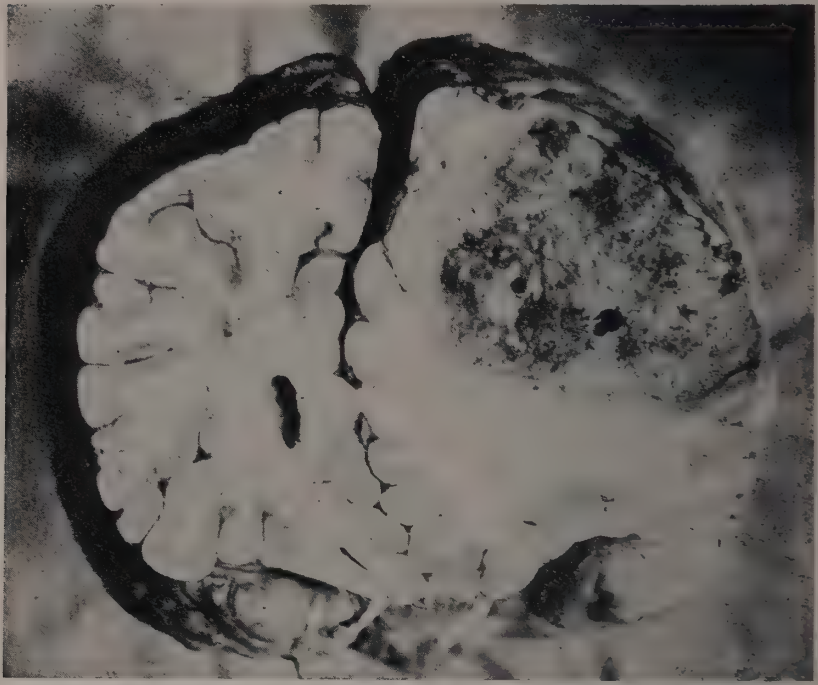


FIG. 36.—Gross appearance of an unclassified tumor, possibly a unipolar neuroblastoma (J. H. H. Surg. No. 22551). Patient aged 45, symptoms of left frontal tumor, seven months' duration. Long antiluetic treatment. Death on the third day after mere exposure of tumor at operation. Complete necropsy. Successive diagnoses: round-cell sarcoma; myeloma; endothelioma; glioma of unusual character.

Although it has proved impossible in this tumor to impregnate the fibrillogenous zone of Held, it seems probable that the cells are apolar neuroblasts for the following reasons: the nuclei resemble those of nerve cells; a few bipolar neuroblasts are present; and there are areas of undifferentiated cells, such as have been found in another tumor in which the differentiation has proceeded far enough so that definite nerve cells may be identified.

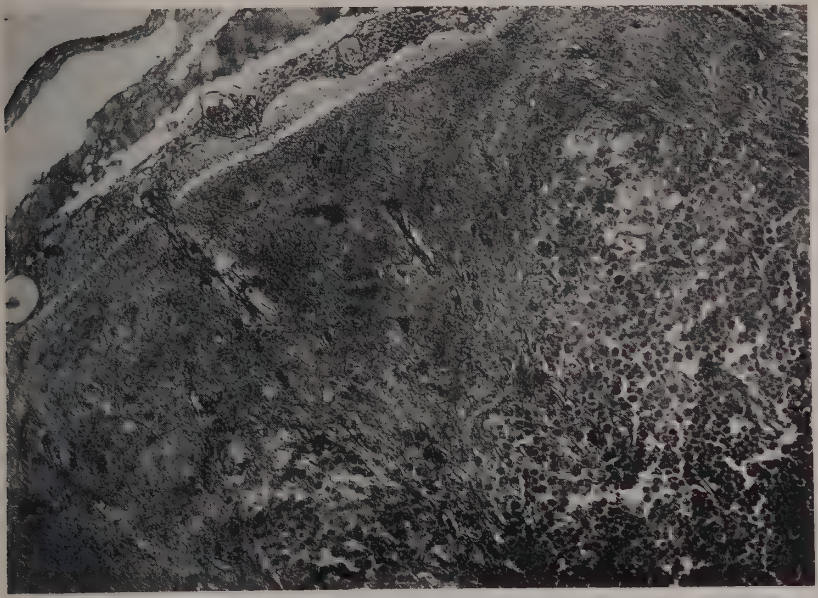


FIG. 37.—Same as Fig. 36. Low power (× 80) section from margin ot tumor. Phosphotungstic acid-hematoxylin stain.

15. BIPOLAR NEUROBLAST.—Bipolar neuroblasts are also rarely encountered, and when found they are scattered among other cells. Their appearance by Cajal's method is shown in Figure 39, a, where two bipolar neuroblasts are to be seen. Under the microscope it is apparent that each has a large vesicular nucleus. With ordinary staining methods they may be distinguished from bipolar spongioblasts by the character of their nuclei and the heavy staining of their cytoplasm.

One would perhaps expect to find such cells more often in the tumors of the spinal ganglia. In a much-quoted article, Friedrich [22] has described a tumor of the retropleural region in which he claims to have demonstrated bipolar neuroblasts. A picture very similar to that illustrated by Friedrich we have observed in a meningeal tumor impregnated by Cajal's method (Fig. 39, b). The result was accidentally obtained by keeping the sections in the silver solution until the method had lost its specificity, which accounts for the fact that the endothelial cells of the capillaries are also impregnated. We are therefore inclined to attribute the results obtained by Friedrich to his having employed a method which was not specific.

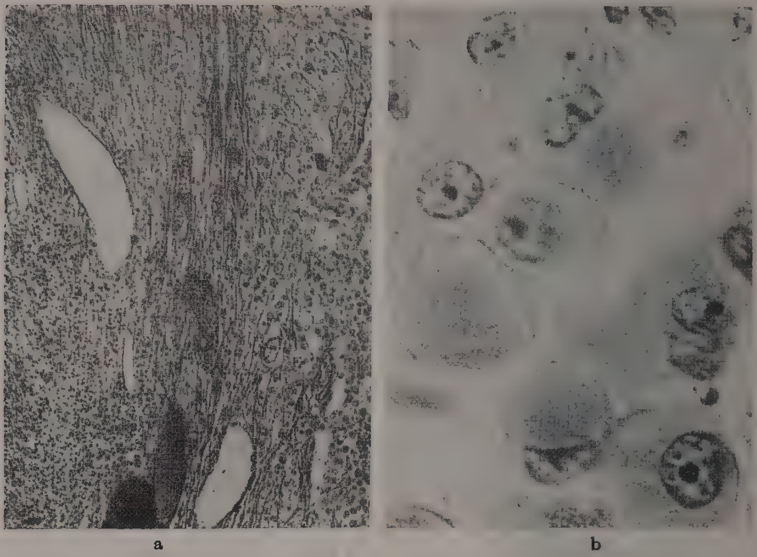


Fig. 38.—Details from tumor shown in Fig. 37. a, Indifferent cells in lower left-hand corner. Phosphotungstic acid-hematoxylin stain. × 80. b, Idem. × 850. Polygonal cells with large nuclei.

16. Unipolar Neuroblast.—Three tumors composed almost wholly of unipolar neuroblasts have been identified. The character of the cells stained by Cajal's reduced-silver method is

unmistakable (Fig. 40; *cf.* also Fig. 81). Their nuclei may or may not show the characteristic change which has been described as occurring when a neuroblast is transformed into a nerve cell. A few unipolar neuroblasts may occasionally be found in a particular tumor of the brain, which will be described later as a medulloblastoma (*cf.* Fig. 50).

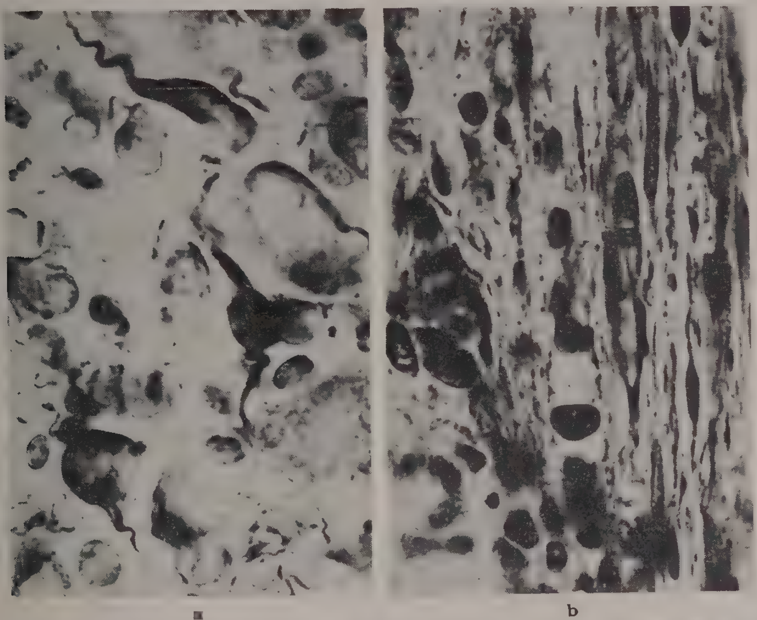


FIG. 39.—a, Surg. No. 11465. Cajal's reduced silver method. × 850. Two bipolar neuroblasts are impregnated. b, Surg. No. 4077. Cajal's reduced silver method. × 850. Meningeal tumor. Overimpregnated. Cytoplasm of bipolar cells is impregnated but they are probably not neuroblasts.

17. MULTIPOLAR NEUROBLASTS.—These neuroblasts, like all the others, are only occasionally seen. We have encountered no tumor largely composed of them. They may or may not have Nissl bodies in their cytoplasm, but the periphery of the cell often contains a granular material which stains like true tigroid substance. Their nuclei have the same characteristics as those of nerve cells, being round and large, with a heavy nucleolus

and scanty chromatin. Numerous amyelinated nerve fibres are given off in various directions. Such a cell, found in a tumor of the occipital lobe, along with many similar cells, as shown in Figure 41, a, is of a type not normally found in the cerebral cortex. The other cell, shown in Figure 41, b, is from a tumor in the spinal region. We have not seen such definite Nissl bodies in neoplastic nerve cells of any of the brain tumors in our series.

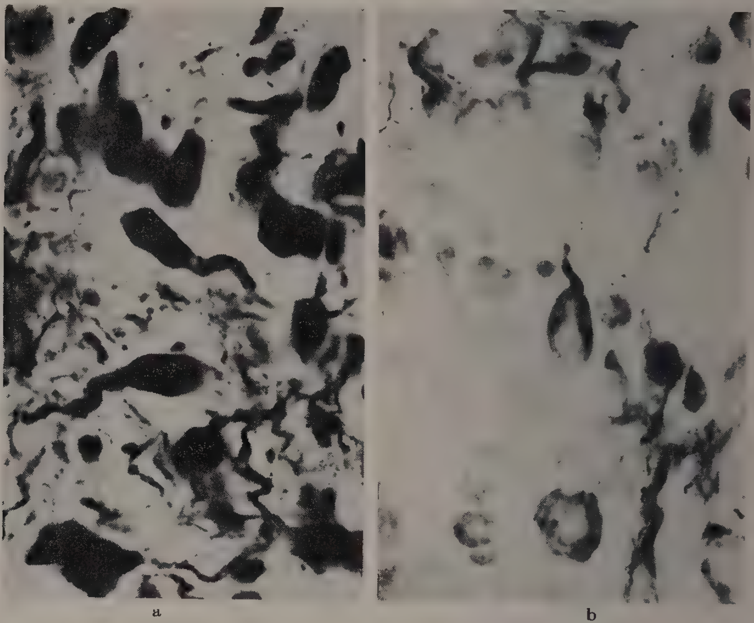


Fig. 40.—Unipolar neuroblasts. a, J. H. H. Surg. No. 20638. Cajal's reduced silver method. × 850. Tissue fixed in formalin for eighteen years. b, Surg. No. 11463. Cajal's reduced silver method. × 850. Fresh tissue.

18. Neurones.—Nerve cells with myelinated nerve fibres and well-marked tigroid substance we have never encountered. Myelin sheaths have been reported by Olivecrona [51] as having been observed in a tumor of the cerebral hemispheres, but it is not certain from his description that they may not have belonged to nerve fibres traversing the tumor from cells in the

normal surrounding brain. Lhermitte and Duclos [39] state that they have observed imperfect myelin sheaths on the processes of the neoplastic nerve cells of a tumor of the cerebellum.

19. Microglia.—As Penfield [52] has pointed out, these cells may occur as scavengers in brain tumors. An impregnation of the microglia in the cortex adjacent to a tumor we have often seen, but the microglial cells extend only as far as the boundary of the neoplasm, and we have not with certainty identified them as neoplastic cells. In one case only (Surg. No. 19986) did we obtain an impregnation of the tumor cells by Hortega's method for the microglia, and it will be briefly described here.

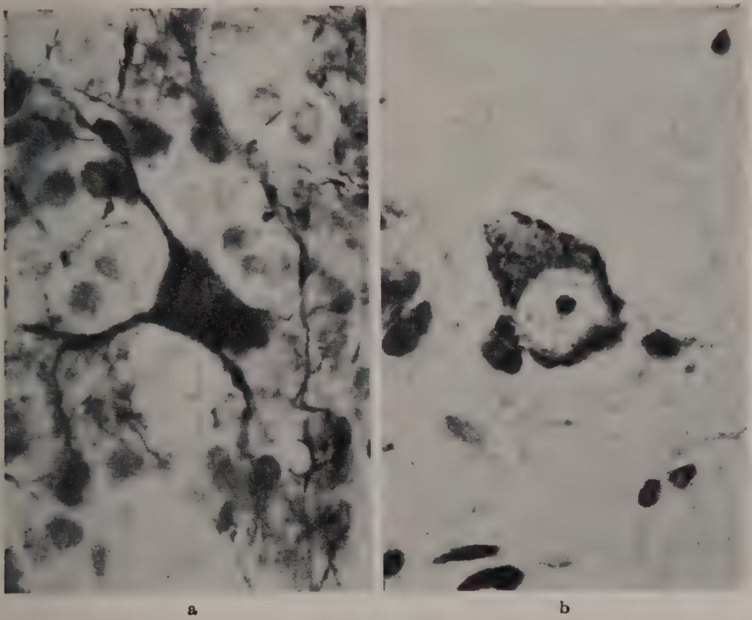


Fig. 41.—Multipolar neuroblasts. a, Surg. No. 11463. Cajal's reduced silver method. × 850. From a cerebral tumor, showing neurofibrillæ. b, Surg. No. 14560. Nissl's method. × 850. From a spinal tumor, showing tigroid substance.

The specimen removed from a tumor of the occipital lobe at operation was fixed both in formalin bromide and in Zenker's fluid. Sections show the tumor to be composed of evenly distributed cells and their processes (Fig. 42). Blood-vessels are rather rare, and the connective tissue is confined to their walls. The cells are of various sizes and shapes. Those with a single nucleus are small, with scanty cytoplasm, but a great number of cells are multinucleated, and upon this the size of the cell seems to depend. The nuclei are elongated, elliptical or kidney-shaped, and have a very heavy chromatin reticulum (Fig. 42, b). The processes are numerous and often corkscrew-shaped. They occasionally branch dichotomously. They are not stained with phosphotungstic acid-hematoxylin, neutral ethyl-violet, nor with Cajal's gold-sublimate. They were very sharply impregnated by Hortega's silver-carbonate method for the microglia on the second day of fixation. The processes usually run around the vascular sinuses without being attached to them. Mitotic figures are few.

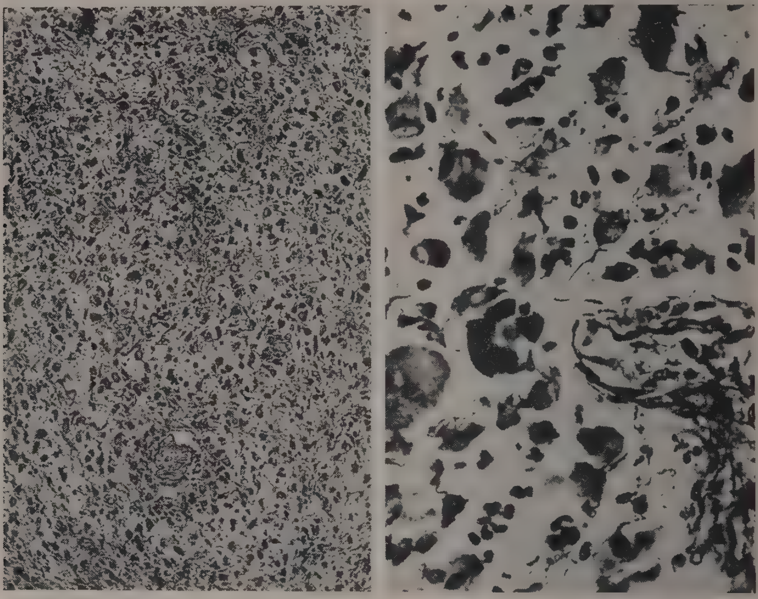

a b

FIG. 42.—Cerebral tumor whose cells were impregnated by the technique for demonstrating the microglia. a, Surg. No. 19986. × 80. Hematoxylin and eosin stain. b, Surg. No. 19986. Hortega's method for microglia. × 850. Note the corkscrew-shaped processes.

From many dozens of attempts, this is the only brain tumor in our series in which cells have been impregnated with the microglial technique. Many times the microglial cells may, as stated, be followed up to the very edge of the tumor, but only in this single instance were they found composing the tumor itself, if indeed these neoplastic cells may actually be microglial. It may be recalled in favor of this view: (1) that the cells were impregnated sharply by the microglial technique; (2) that they were not impregnated by methods specific for neuroglial cells; (3) that the tumor is one of very unusual structure, unique in the series; and (4) that the nuclei closely resemble those of microglial cells. Against this view might be urged: (1) that the processes do not show the lateral excrescences characteristic of microglial cells; (2) that the processes of some of the cells are attached to the vessel walls in a manner similar to "sucker feet"; and (3) that the tumor is but an isolated example with no confirmatory evidence. The observation is submitted merely for the reason that it is the only evidence found in this study that the microglia may participate in the formation of a brain tumor.

Roussy, Lhermitte, and Cornil [62] state that certain cellular gliomas (*gliomes cellulaires ou afibrillaires*) are due to the proliferation of the microglia, without, however, presenting any evidence in favor of this statement. Their views are doubtless colored by their belief that the microglia is a type of neuroglia and not, as Hortega thinks, a specific tissue derived from the mesoderm. Since the microglial cells have very definite structural characteristics, it seems to us not permissible to state that a tumor is derived from them unless its cells show the peculiarities possessed by the normal microglial cells.

20. Choroidal Epithelium.—The vascular tufts of papillomata of the choroid plexus are covered by cells of this character. They do not occur in other tumors, and, as already stated, are only included in this discussion of the gliomas because

of their histogenetic origin from the medullary epithelium. The cells may be somewhat more columnar in shape than the normal. They contain mitochondrial granules, just as do also the normal choroidal cells, and can only be distinguished from ependymal cells by the absence of blepharoplasten. Their nature is shown in the accompanying photographs (Fig. 43).

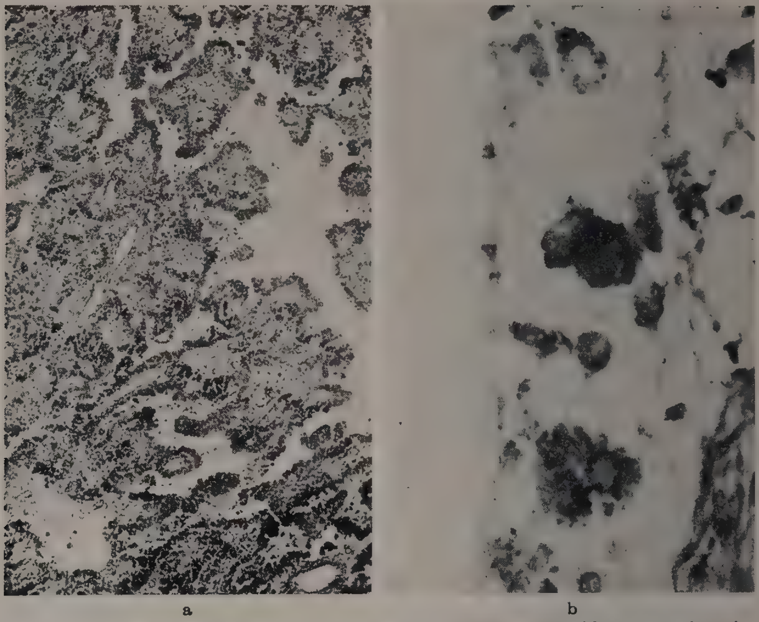


Fig. 43.—Papilloma chorioideum. a, J. H. H. Surg. No. 23506. Aniline blue-orange G. stain. × 80. b, Detail from "a." Phosphotungstic acid-hematoxylin stain. × 850. Cells filled with coarse mitochondria.

E. A CLASSIFICATION OF THE GLIOMATA

It has been shown in a preceding section how each of the twenty different cellular types may be identified with greater or less frequency in the tumors originating in the brain. But it must be remembered that such cellular types are abstractions from a continuous development, and it is not to be expected that neoplastic cells will reproduce the structure of these types accurately, when the types themselves represent merely a transitory stage through which certain cells pass in their normal development within the nervous system.

That gliomas are rarely found to be composed of a single type of cell should be no cause for surprise. The situation is the same as that which obtains in the case of other tumors. Mallory [41] has explained, for example, how the ordinary connective-tissue cell, the fibroblast, not only produces both fibroglia and collagen fibrils, but has inherent in it the property also of being able to manufacture certain other substances. Thus in many situations the fibroblast gives origin to elastic fibrils, and under other circumstances it may also produce three different kinds of homogeneous substances, namely, mucin, chondromucin, and osseomucin. Hence connective-tissue tumors frequently show curious combinations and proportions of fibrils and intercellular substances, and thus the formation of an osteo-chondro-myxo-fibroma becomes readily comprehensible.

For similar reasons a brain tumor which happens to arise from a group of medulloblasts (the indifferent cells of Schaper) may contain protoplasmic and fibrillary neuroglia, oligodendroglia, and neurones, in addition to medulloblasts, spongioblasts, and neuroblasts in various stages of development. But in spite of the possibility for infinite variation in composition and for the existence of transitional forms, a careful study, not only of the literature but of our own long series of cases, has convinced us that with few exceptions the true brain tumors may be classified under fourteen major categories as follows:

TABLE II. TUMOR CLASSIFICATION.

1. Medullo-epithelioma.
2. Medulloblastoma.
3. Pineoblastoma.
4. Pinealoma.
5. Ependymoblastoma.
6. Ependymoma.
7. Neuro-epithelioma.
8. Spongioblastoma, (a) multiforme, (b) unipolare.
9. Astroblastoma.
10. Astrocytoma, (a) protoplasmaticum, (b) fibrillare.
11. Oligodendroglioma.
12. Neuroblastoma.
13. Ganglioneuroma.
14. Papilloma chorioideum.

1. MEDULLO-EPITHELIOMA.—Only two tumors were found which might with justice be so designated. One of them took its origin from the post-infundibular region of the floor-plate of the third ventricle. It was a very rapidly growing tumor, with numerous mitoses. The cells, as heretofore mentioned (p. 27), tended to grow in long bands with limiting membranes, through which the cells had broken in numerous places to form irregular masses (Fig. 44, a). They had also invaded the brain along the spaces of Virchow-Robin, but a complete necropsy showed no metastases. A tumor of very similar nature which originated in the pars ciliaris retinæ has been described by Emanuel,[18] whose illustration is reproduced for comparison (Fig. 44, b).

The second tumor, of somewhat different structure, but doubtless of the same nature, occurred in the midbrain (*cf.* Fig. 84). Its exact point of origin could not be determined, but the pineal body lies distinct from it. The growth extended deeply into the vermis of the cerebellum, into the third ventricle, and into the right cerebral hemisphere, but was everywhere sharply separated from the brain substance. In all probability it arose from the roof-plate somewhere in the region of the pineal body or between the cerebellum and corpora quadrigemina.

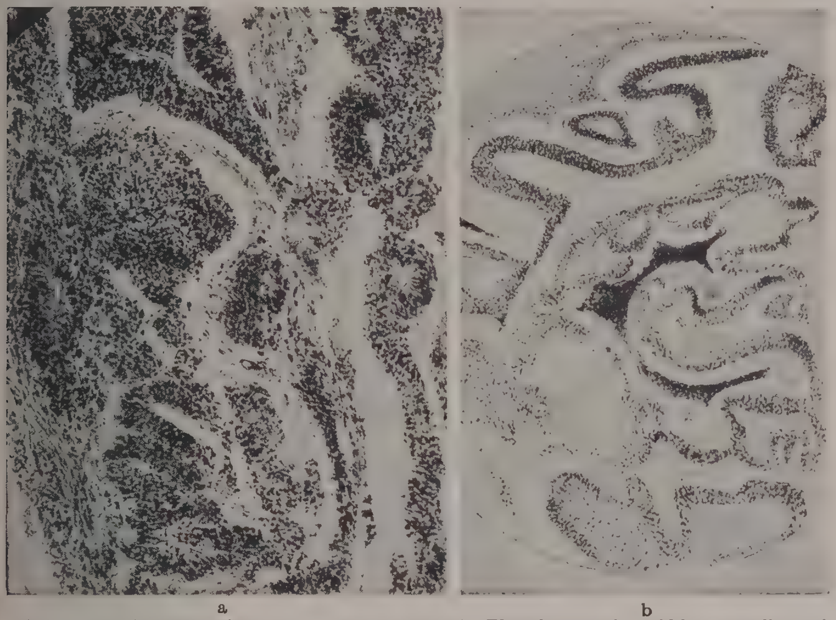


FIG. 44.—a, Medullo-epithelioma. Surg. No. 17041. Phosphotungstic acid-hematoxylin stain. × 80. In this area the cells have broken through the basement membranes shown in Fig. 19, and are growing diffusely. In the middle of the right-hand margin is seen the canal enlarged in Fig. 20. b, Tumor of the pars ciliaris retinæ. (After Emanuel.)

Microscopically this tumor is composed of epithelial cells with well-defined cell boundaries. There is no fibrillary material of any sort. The cells have abundant cytoplasm, oval nuclei, and are columnar in shape when they radiate from the numerous small vascular sinuses (Figs. 45, a and 46); elsewhere they are spindle-shaped. Mitotic figures are exceedingly numerous (Fig. 45, b) and in most of the cells the microscope detects a minute diplosome, surrounded by a clear halo.

Our two tumors, and that of Emanuel, grew from the only regions where the original medullary epithelium remains undifferentiated, namely, from the pars ciliaris retinæ, and from the roof- and floor-plates of the brain.

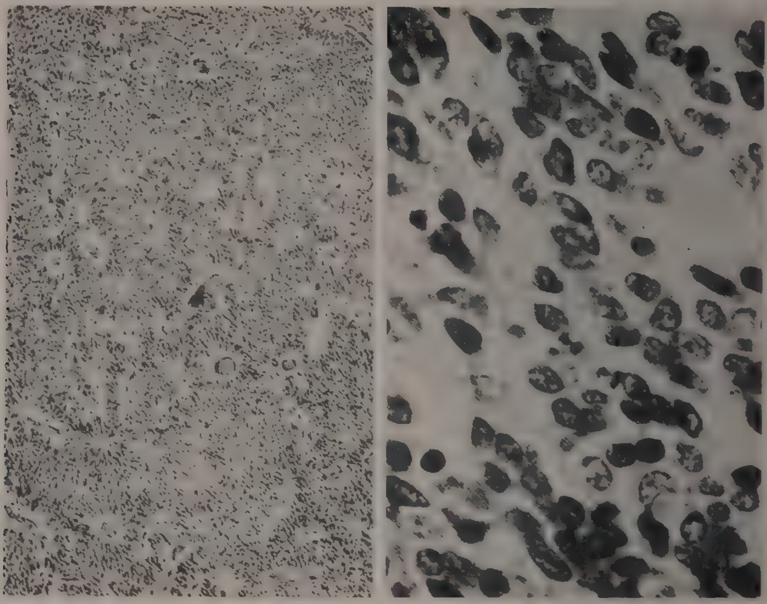

a b

Fig. 45.—Medullo-epithelioma. Surg. No. 17549. a, Methylene blue eosin stain. × 80. Cells radiate around vascular sinuses. b, Same stain. × 850. There are five mitotic figures in this small field.

2. Medulloblastoma.—Arising in various places in the central nervous system, but most commonly in the cerebellum of children, is found a very cellular tumor containing numerous mitotic figures. The typical cells of these tumors contain round or slightly oval nuclei with abundant chromatin; their cytoplasm

is scanty, and either surrounds the nucleus in a ring, or streams away from one pole in an indefinite tail. Ordinarily the cells do not assume any characteristic arrangement, though they may collect in groups forming a pseudo-adenomatous structure (Fig. 47, a), or may form the pseudo-rosettes we have already spoken of as common in sympathicoblastomas (Fig. 47, b), or may align themselves in long rows (Fig. 48, a). Between the nuclei lie the tails of the cells, which as a rule will not stain either for neuroglia, nerve fibres, or connective tissue.

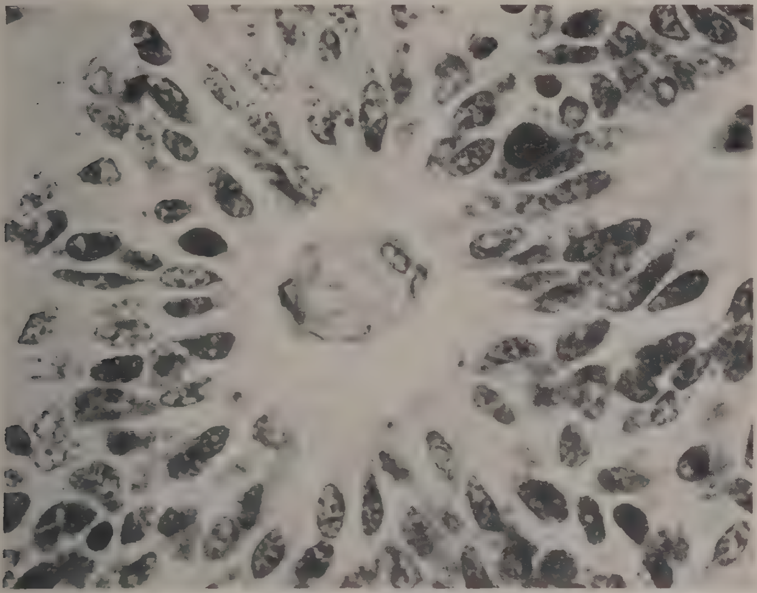


Fig. 46.—Perivascular pseudo-rosette. Detail from tumor shown in Fig. 45. Surg. No. 17549. Methylene blue eosin stain. × 850.

Although the small amount of connective tissue which is present is usually confined to the walls of the numerous small vascular channels (Fig. 48, b), sprouts of connective tissue may pass between these thin vessels. This tendency to the formation of a stroma, pointed out by S. B. Wolbach,[75] has also been noted by Vanzetti,[70] but it is far more characteristic of the rare tumors we are to describe as true neuroblastomas (page 128) than of the neoplasms now under consideration.

In nearly all of these medulloblastomas will be found, in one place or another numerous spongioblasts, which are best demonstrated by Hortega's 4th variant (Fig. 49); and the spongioblast depicted in Figure 31, d, was from one of these tumors. Sometimes the cells are sufficiently differentiated to stain with methods for neuroglial fibrillæ, and the differentiation may even proceed to the formation of astrocytes.

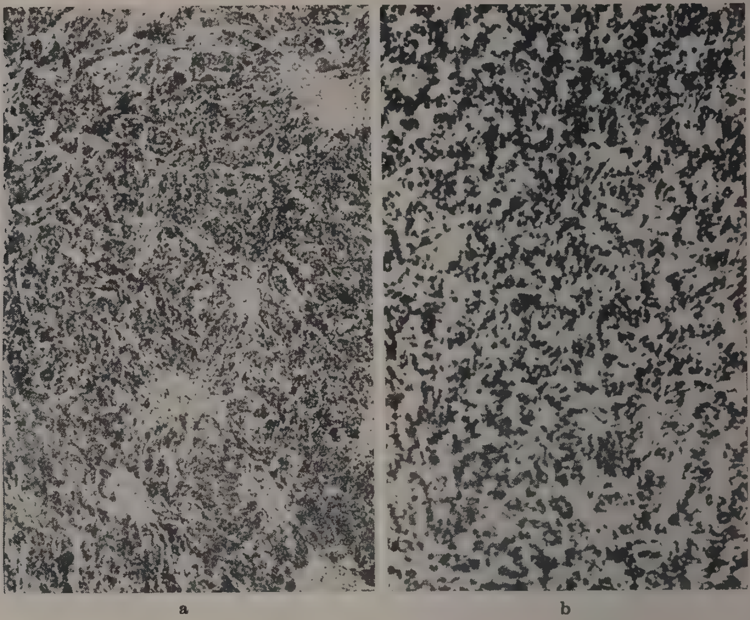


Fig. 47.—Medulloblastoma. a, Surg. No. 3676. Phosphotungstic acid-hematoxylin stain. × 80. Primary focus in cerebrum. "Adenomatous" structure identical with that of the *rétinocytome sans stéphanocytes* of Mawas. b, Later extension of tumor showing pseudo-rosettes. Hematoxylin and eosin stain. × 80.

Lying scattered among the smaller cells neuroblasts also may occasionally be identified by the character of their large vesicular nuclei, which have almost no chromatin and a heavy nucleolus (Figs. 50, b and 51, b). When a region in which neuroblasts occur is stained by Nissl's method, the cytoplasm surrounding these nuclei stands out in sharp contrast to the other cells (Fig. 50, a), and Cajal's method discloses fine unmedullated processes coming off from the deeply stained cytoplasm (Figs. 51, a and 52, a). Rarely a tumor may be seen which, in addition to the abundant medulloblasts, shows an occasional neuroblast but no spongioblasts (Fig. 50, b). Vanzetti[70] has reported one of these unusual cases, but it is more common for a medulloblastoma to contain cells of both types, as shown in Figure 52.

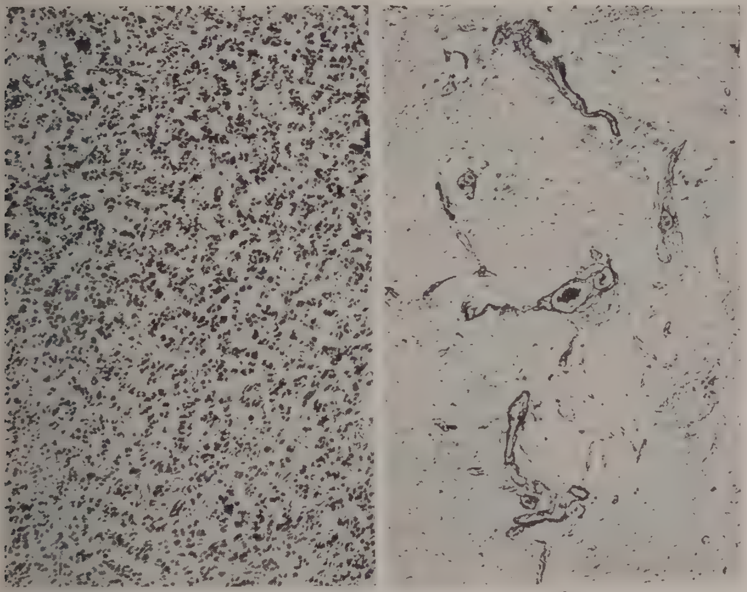

a b

FIG. 48.—Medulloblastoma. a, Surg. No. 17669. Neutral ethyl violet-orange G. × 80. Nuclei arranged in palisades. b, Surg. No. 11785. Perdrau's method. × 80. Connective tissue confined to walls of vascular sinuses.

Since, therefore, both neuroblasts and spongioblasts are occasionally found in these tumors, it seems probable that the cells which compose their bulk are bipotential, and represent the antecedent stage of development corresponding to the indifferent cells of Schaper, in other words to what we call medulloblasts.

These medulloblastomas are liable to become disseminated by implantation throughout the subarachnoid spaces. The appearance of such a tumor, which spread widely down the spinal cord, is shown in Figure 53. In this instance the implanted tumor has lost its original architectural arrangement (*cf.* Fig. 47, a and Fig. 53, b) and one is totally unable to find spongioblasts in the implantation, the cells of which are completely undifferentiated, whereas spongioblasts are easily found in the original focus in the brain.

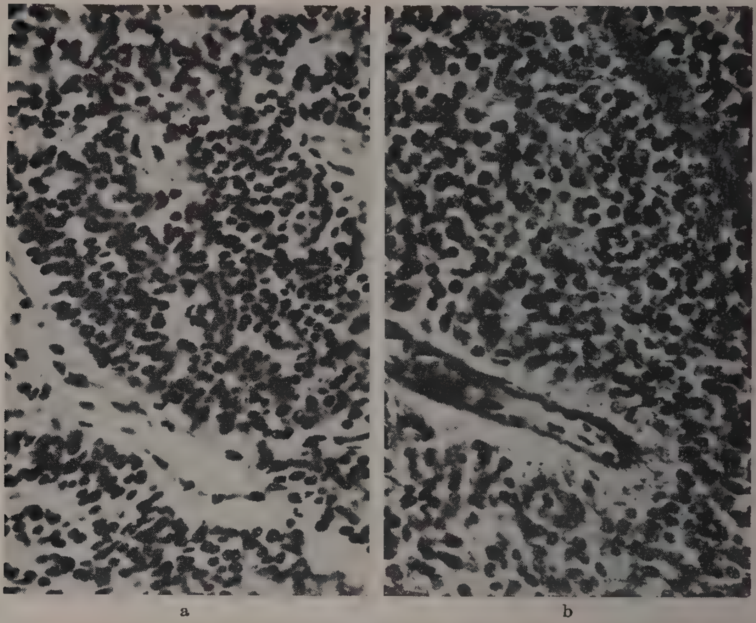


FIG. 49.—Successive sections from a medulloblastoma gliomatosum impregnated by two methods. Surg. No. 2175. a, Cajal's reduced silver method. × 300. No evidence of neurofibrillæ. b, Hortega's fourth variant. × 300. Delicate processes of spongioblasts are impregnated.

The small round-celled tumors which thus "infect" the subarachnoid space are usually described as "sarcomatosis" of the meninges, but it has been pointed out by Strassner, Fischer, Rach, and many others that they are of medullary origin in most cases. There seem, however, to be a few authentic examples of such diffuse meningeal tumors in the absence of a primary growth in the central nervous system. Such tumors may doubtless take their origin in the leptomeninges, whose formation out of cells migrating from the ganglionic crest has recently been disclosed by Harvey and Burr.[29] On this basis they would be closely allied to the other diffuse tumors of medullary origin, but since they arise from the anlage of the leptomeninges, they should be excluded from the brain tumors proper and be rele-

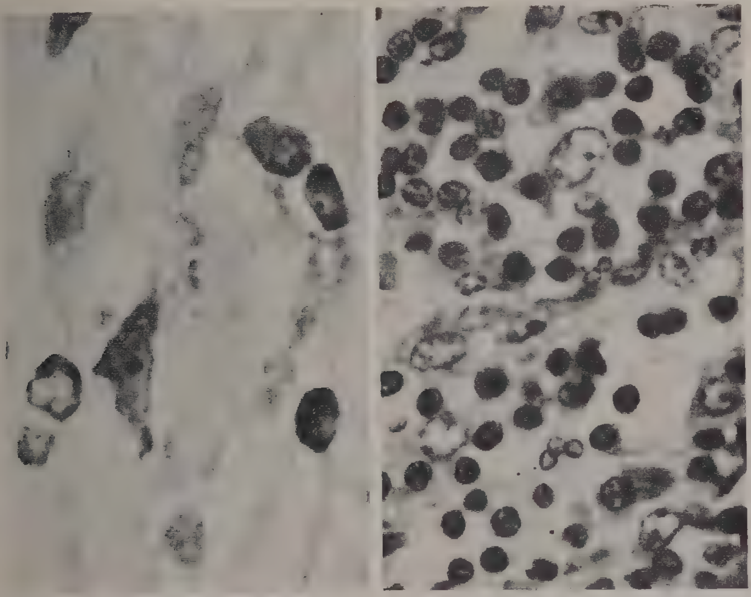

a b

FIG. 50.—Medulloblastoma neuromatosum. J. H. H. Surg. No. 28084. a, Nissl's method. × 850. The cytoplasm of the neuroblasts alone is stained. b, Hematoxylin and eosin stain. × 850. Note the vesicular nuclei of the neuroblasts.

gated to the group of meningeal tumors under the term *meningoblastoma,* proposed for them by Oberling.[49]

A very similar tumor is also found in the retina, where it has long been known as glioma retinæ, a term with which pathológists have been dissatisfied; and Treacher Collins [13] has pointed out the resemblance of the neoplastic cells to those of the undifferentiated retina of the fœtus at about the third month. This resemblance has been generally observed, and a French pathologist, Mawas,[45] has used the term *rétinocytomes* for these lesions, but to adhere to the terminology herein adopted, *retinoblastoma* would be preferable. The tumor would then be analogous to the medulloblastomas and meningoblastomas just mentioned, and one would naturally expect to find occasional

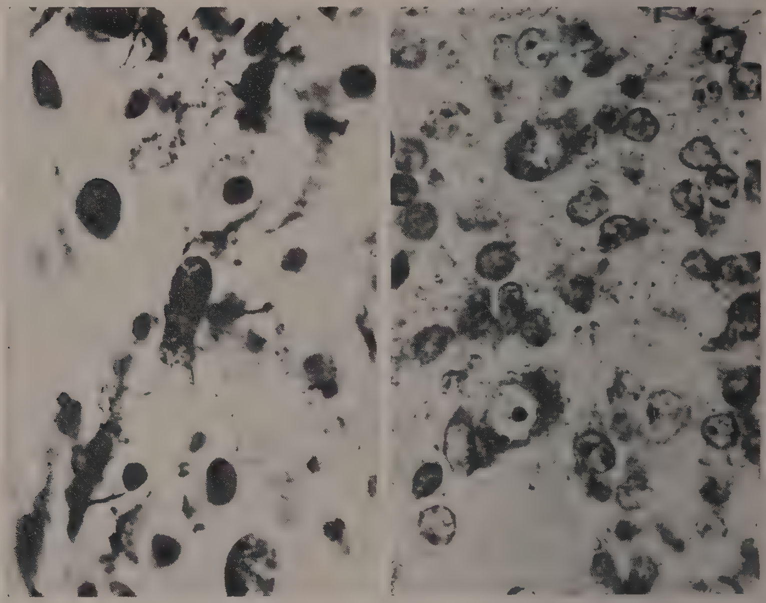


FIG. 51.—Medulloblastoma neuromatosum. a, J. H. H. Surg. No. 28084. Cajal's reduced silver method. × 850. Unmyelinated processes are impregnated. b, Surg. No. 16059. Methylene blue eosin stain. × 850. Neuroblasts may be identified by their large vesicular nuclei.

nerve cells, as described by Greef,[25] or neuroglia, as described by Redslob,[58] or even a tumor composed almost entirely of neuroglial cells, such as the *angiogliomatose retinæ* of von Hippel.

The same possibilities exist with the sympathetic nervous system, where very cellular and rapidly growing tumors arise, generally known as neurocytoma or neuroblastoma, terms given to them by Wright.[76] Neuroblasts may differentiate in such tumors as shown by Robertson[60] and others, but certainly not all the neoplastic cells are potentially neuroblasts, for some of them may differentiate into chromaffin cells similar to those in the adrenal medulla. The cells which form the characteristic "balls" resemble capsule cells more than nerve cells, and one may

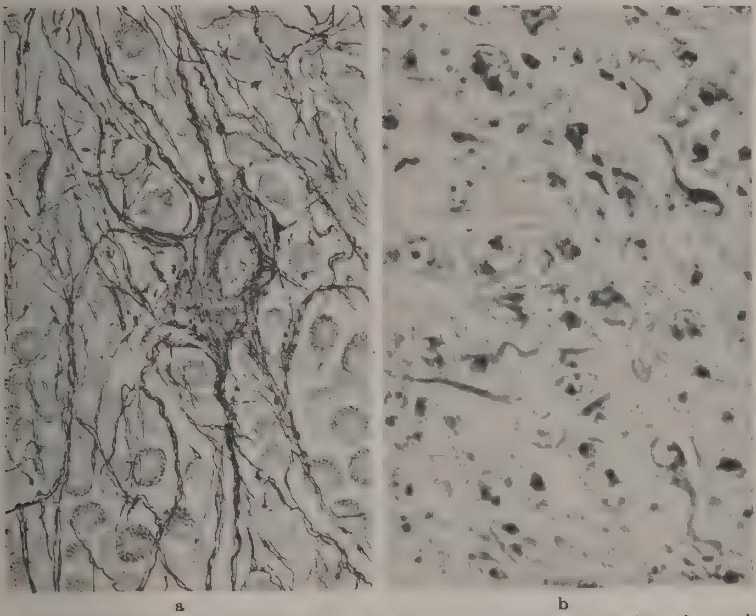


FIG. 52.—Medulloblastoma glianeuromatosum. Surg. No. 11463. a, Drawing of a multipolar neuroblast. Cajal's reduced silver method. × 850. b, Neutral ethyl violet-orange G. stain. × 850. Unipolar spongioblasts are stained.

imagine that their arrangement in pseudo-rosettes is an expression of their inherent tendency to form capsules for the ganglion cells. The term "neurocytoma" is exact if one employs it in the sense of the neurocyte of Kohn, that is to say, a wandering cell from the ganglionic crest which has not differentiated. But even so, the term seems to imply that the cells are potentially nerve cells, and the indifferent term *sympathicoblastoma* would therefore seem more appropriate.

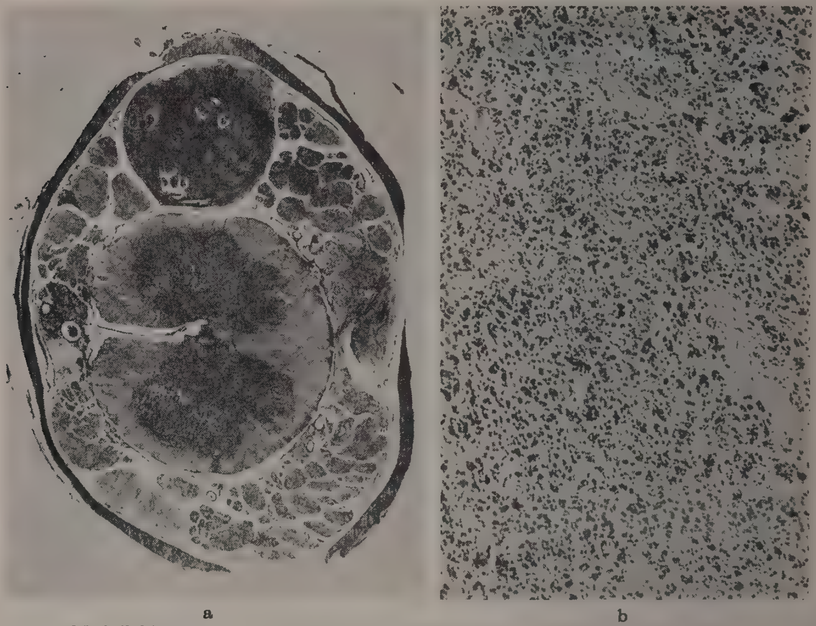


Fig. 53.—Medulloblastoma. a, Invasion of the spinal meninges. Phosphotungstic acid-hematoxylin stain. ×9. b, Van Giesen-Weigert stain. ×80. Enlargement of tumor seen in meninges in "a".

All of these tumors, medulloblastoma, retinoblastoma, meningoblastoma, and sympathicoblastoma, become from this point of view analogous, being composed of pluripotential cells from various portions of the anlage of the nervous system, which explains the similarity of their structure.

We may therefore define one of these tumors as a rapidly growing cellular lesion composed mainly of medulloblasts, but in which neuroblasts, spongioblasts, or both, may be differentiated. Qualifying adjectives may be added, depending on whether spongioblasts, neuroblasts, or both, are differentiated in the tumor, thus medulloblastoma, medulloblastoma gliomatosum, medulloblastoma neuromatosum, medulloblastoma glianeuromatosum.

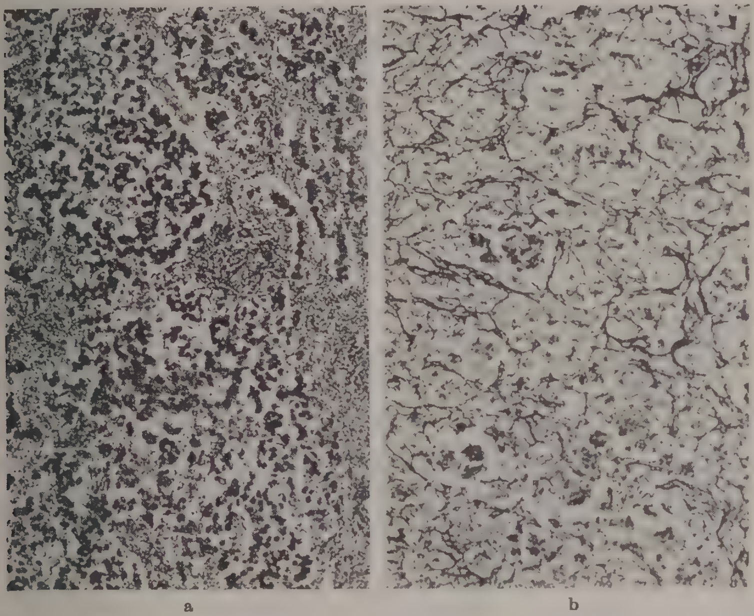


FIG. 54.—Pinealoma. Surg. No. 21567. a, Hematoxylin and eosin stain. × 80. Characteristic appearance of pinealoma; groups of large cells separated by areas of lymphoid cells. b, Perdrau's method. × 80. Reticulum of lymphoid cells is shown.

3. PINEOBLASTOMA.—In a paper from this clinic by Horrax and Bailey[33] there were described several very cellular and rapidly growing tumors in the pineal region in which spongioblasts were found, but no neuroblasts. They are closely allied to the medulloblastomas of the previous section, differing only

in that they contain no potential neuroblasts. They resemble in structure the anlage of the pineal body (*cf.* Fig. 22), which is also incapable of giving origin to nerve cells. Though the neoplasms were described under the term of "pinealomas of spongioblastic type," it seems better to reserve the term "pinealoma" for more highly differentiated tumors, and to speak of these growths simply as *pineoblastomas.*

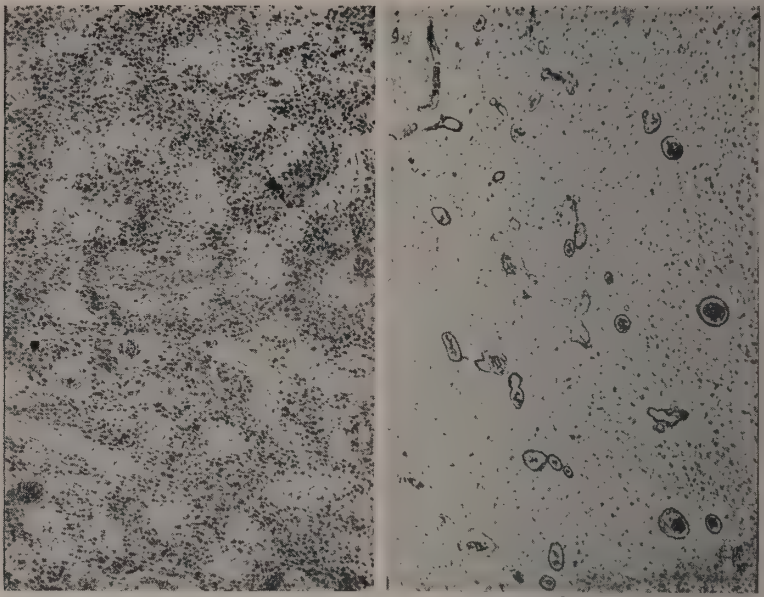


Fig. 55.—Ependymoblastoma. Surg. No. 14560. a. Methylene blue eosin stain. ×80. Characteristic clear areas around the vessels. b, Perdrau's method. ×80. Connective tissue is confined to the vessels.

4. Pinealoma.—These tumors have a characteristic structure, the neoplastic cells composing the main body of the growth being divided into groups by a connective-tissue reticulum (Fig. 54, b), in the meshes of which are numerous small lymphoid cells (Fig. 54, a). The nests of the tumor cells, which lie in loose masses, are large and spherical, with huge vesicular nuclei,

representing imperfectly differentiated cells of the pineal parenchyma, and may show processes ending in typical bulbs (*cf.* Fig. 23, b). Occasionally a neuroglial cell may be identified among the tumor cells, and in certain rare cases, as in that reported by Raymond and Claude,[57] they may actually be the predominating element.

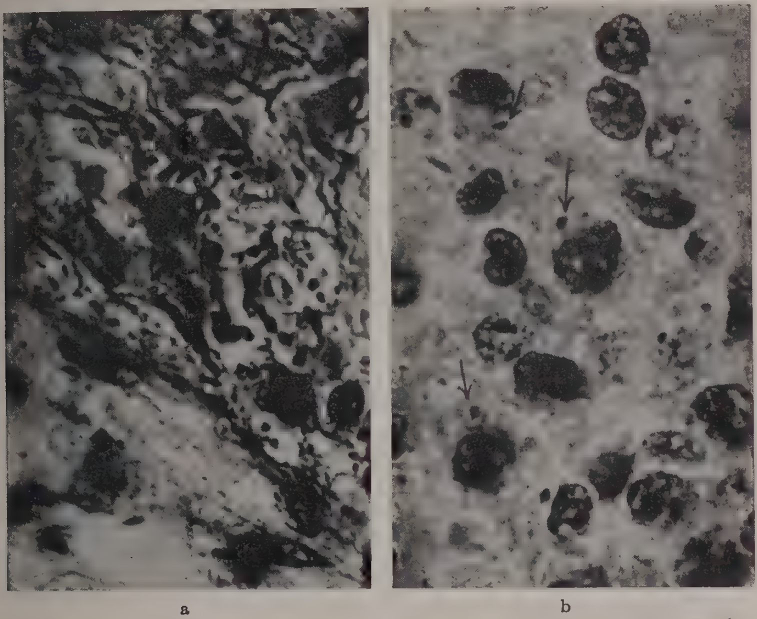


Fig. 56.—Ependymoblastoma. Surg. No. 14560. a, Phosphotungstic acid-hematoxylin stain. × 850. Tails of cells are shown, filling the perivascular areas which appear clear in Fig. 55a. b, Neutral ethyl violet-orange G. stain. × 850. Blepharoplasten indicated by arrows.

5. Ependymoblastoma.—Of the tumors which reproduce the structure of the ependymal cells, it seems best to make two groups, which were described together in a previous communication by one of us (Bailey[2]) under the name of "ependymoma."

The typical cell of the first group, which will be called *ependymoblastomata,* is depicted in Figure 28, b. Tumors composed of these ependymal spongioblasts have a characteristic structure even under a low magnification (Fig. 55, a). Over the field are scattered small vascular channels (Fig. 55, b), around which are clear areas, surrounded again by the closely packed nuclei. Mitotic figures are almost never found. When the sections are stained with phosphotungstic acid-hematoxylin the " clear " areas around the vessels disappear and are found to be filled with the coarse extremities of the cells (Fig. 56, a). In the cytoplasm of the cells occur blepharoplasten, which lie in a group surrounded by a clear area (Fig. 56, b).

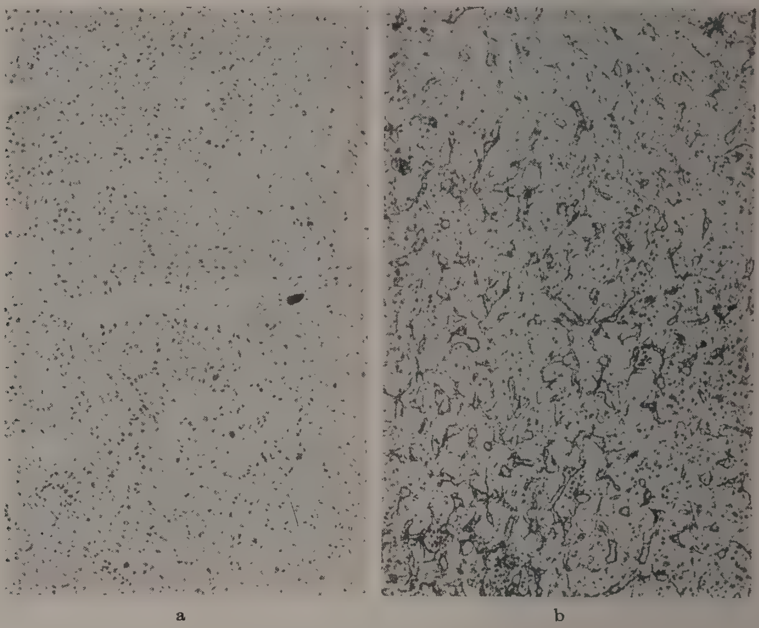
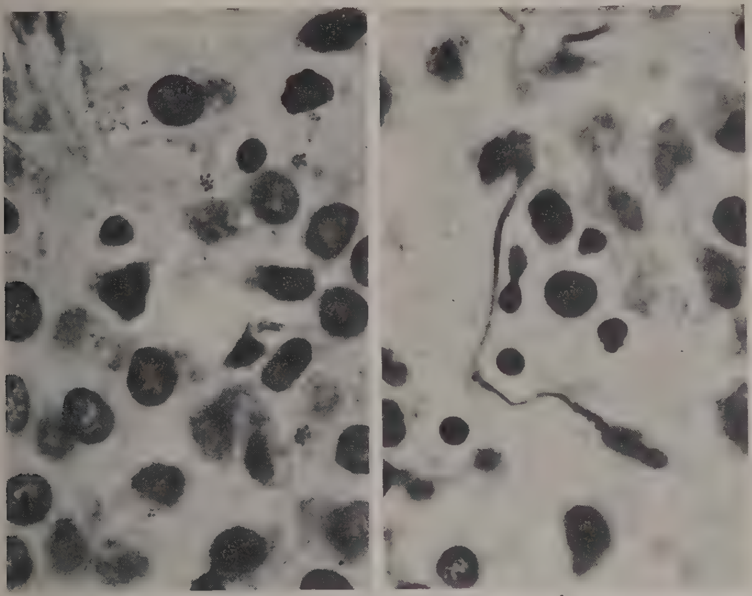


Fig. 57.—Ependymoma. a, Surg. No. 4764. Neutral ethyl violet-orange G. stain. × 80. b, Surg. No. 13429. Perdrau's method. × 80. Connective tissue of vessel walls forms a kind of stroma.

6. Ependymoma.—A typical example of this type of tumor, which originated in the fourth ventricle of a child, is shown in Figure 57, a. Since only a few paraffin sections were available for study it was impossible to make Perdrau preparations, but the connective-tissue framework of a similar tumor arising from

the septum pellucidum is shown in Figure 57, b. The stroma of the tumors is characteristic and abundant, as S. B. Wolbach[75] has emphasized. The cells of the ependymomas differ from those of the preceding class, in that they are polygonal and have no tails, but resemble them in that they also show characteristic blepharoplasten (Fig. 58, a). Occasionally an ependymal spongioblast will be found (Fig. 58, b).



a b

FIG. 58.—Ependymoma. Surg. No. 4764. a, Neutral ethyl violet-orange G. stain. × 850. Blepharoplasten in cells. b, Same stain. × 850. One ependymal spongioblast is stained.

7. Neuro-epithelioma.—This type, of which no example occurs in the series, is composed principally of primitive spongioblasts, and is rarely observed in the brain, although primitive spongioblasts, as we have already stated, may occasionally be found in other tumors. Roussy, Lhermitte, and Cornil[62] have described a tumor from the region of the aqueduct

of Sylvius, which may be of this nature, but they give no minute description of the neoplastic cells (Fig. 59, b). Ribbert[59] has described another rather complex tumor composed of primitive spongioblasts and analogous cells, which he calls a "spongio-neuroblastom."

It is characteristic of primitive spongioblasts that they arrange themselves around small cavities known as rosettes. A typical example from the spinal cord is described by Rosenthal[61] under the term "neuro-epithelioma gliomatosum microcysticum" (Fig. 59, a). The tumor was composed almost wholly of primitive spongioblasts surrounding cystic spaces, the intercystic areas being filled with the tails of these cells. Marburg[42] described a similar tumor, also found in the spinal cord, under the name of "blastoma ependymale," and

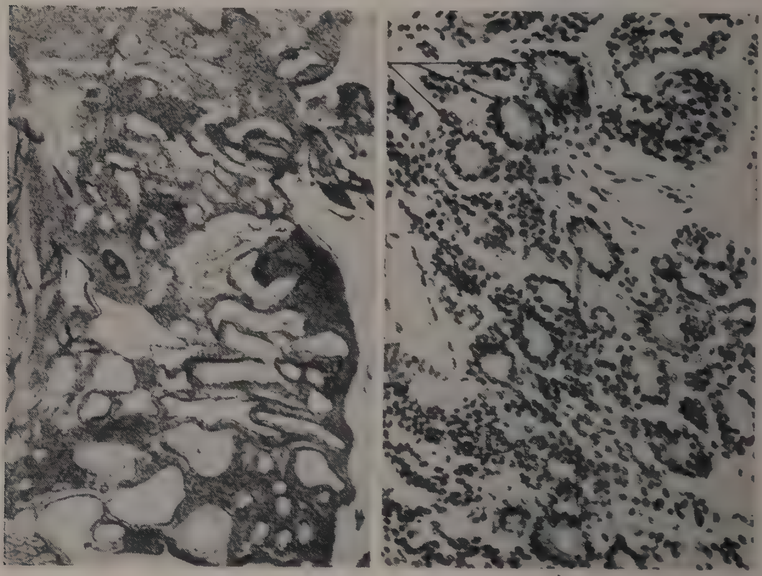


FIG. 59.—a, Copied from Rosenthal. Neuro-epithelioma of spinal cord. b, Copied from Roussy, Lhermitte and Cornil. Neuro-epithelioma (?) of cerebrum.

says that the growth was composed of Cajal's primitive spongioblasts, in other words, cells of neuro-epithelial nature. The typical cells in his tumor were those which surrounded the canals and bore cilia and blepharoplasten at their inner ends with a long process at the other. Benda and Bittorf[5] have also reported similar lesions as occurring in the spinal cord.

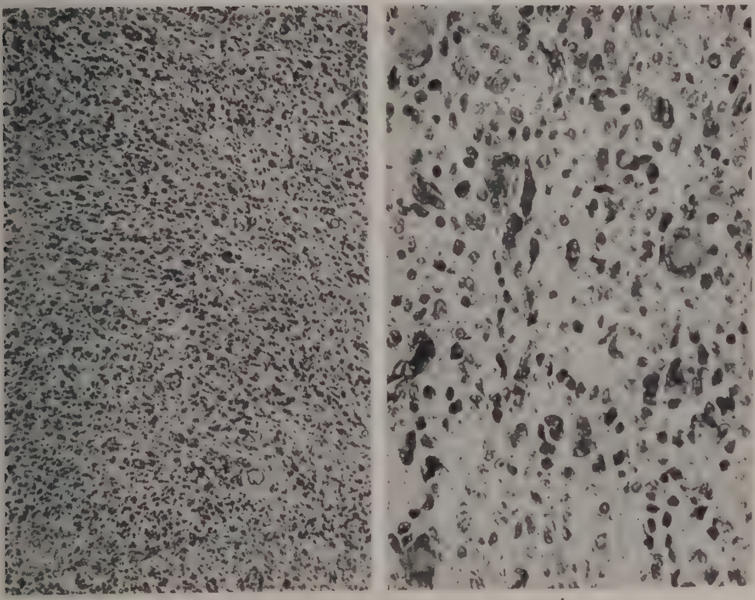


Fig. 60.—Spongioblastoma multiforme. a, Surg. No. 18670. Phosphotungstic acid-hematoxylin stain. ×80. Customary appearance at low magnification. b, Showing numerous true neoplastic giant cells. J. H. H. Surg. No. 18512. Phosphotungstic acid-hematoxylin stain. ×300.

In this category belongs also the retinal glioma characterized by rosettes, variously called "neuro-epithelioma retinæ" by Flexner,[20] a term adopted by Wintersteiner,[73] and "rétinocytome à stéphanocytes" by Mawas. As already explained, the cells of the rosettes are considered to be embryonic rods and cones, hence the term neuro-epithelioma, from the neuro-epithelium of Schwalbe. Ginsberg,[23] however, regards them as undifferentiated embryonic cells representing the germ of the tumor. Against this view may be urged: (1) that in many very early tumors no rosettes can be found; (2) that rosettes occur in metastases; and finally (3) that the tumors containing rosettes, according to Mawas, are the least malignant.

On the whole, it seems more probable that the cells of the rosettes are primitive spongioblasts comparable to the cells of Müller, perhaps even at times embryonic rods and cones, and are therefore a product of differentiation in the tumor, an hypothesis which explains at once the structure of the growth and the lowered malignancy of the neoplasms in which they are found. From this point of view one would have a " spongioblastoma primitivum retinæ " comparable to the " spongioblas-

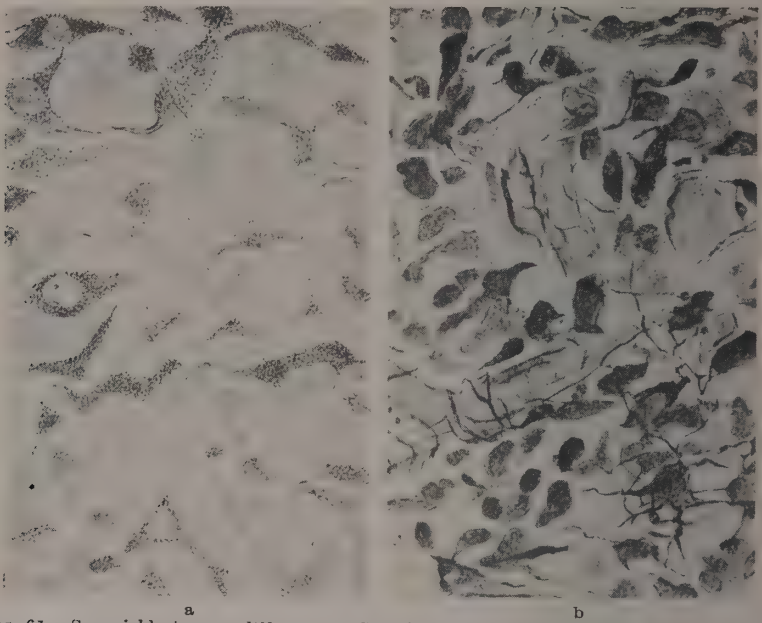


Fig. 61 —Spongioblastoma multiforme. a, Surg. No. 18670. Drawing from gold-sublimate preparation. X 850. Bipolar and bizarre shaped cells are shown. b, Surg. No. 19329. Drawing from gold-sublimate preparation. X 850. One imperfectly developed astrocyte is seen in the lower part of the field.

toma primitivum medullæ spinalis," but the less cumbersome term *neuro-epithelioma* is so well established in the literature that it seems preferable to retain it (*cf.* Note p. 95).

8. SPONGIOBLASTOMA.—In addition to the somewhat rare tumors made up of primitive spongioblasts just described under the name of neuro-epitheliomata, there are two other varieties composed of slightly more differentiated cells in this same line of development, which may be designated as *Spongioblastoma multiforme* and *Spongioblastoma unipolare*.

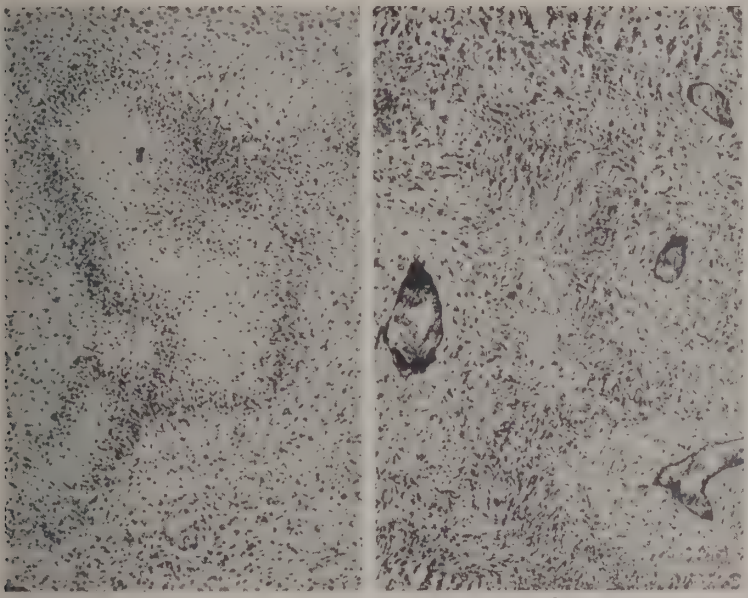


FIG. 62.—Spongioblastoma multiforme. a, Surg. No. 5423. Hematoxylin and eosin stain. ×80. Pseudo-palisade due to necrosis. b, Surg. No. 12204. Hematoxylin and eosin stain. ×80. Showing palisade arrangement of unipolar spongioblasts.

(a) *Spongioblastoma multiforme.*—This is a rapidly growing malignant tumor known formerly as sarcoma or gliosarcoma of the brain, and for which Borst proposed the term "glioma sarcomatodes." Recognizing as others have done that the neoplastic cells are of neuroglial nature, Strauss and Globus,[67] and later Ribbert, proposed the term spongioblastoma. In a recent review Roussy, Lhermitte, and Cornil[62] refer to these lesions as glioma *multiforme,* a term which is eminently suitable, for their striking feature is their multiform aspect. The tumors are prone to undergo degenerative changes, but if an undegenerated area is examined, the cells are seen to lie closely together without any characteristic architectural arrangement (Fig. 60, a).

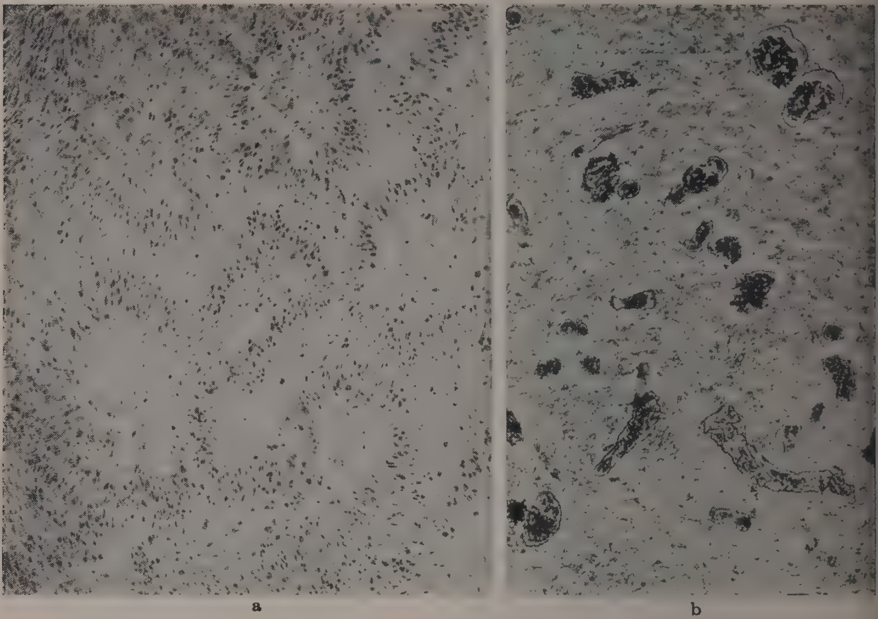


Fig. 63.—Spongioblastoma multiforme. a, Perivascular arrangement due to necrosis. Surg. No. 15434. Methylene blue eosin stain. × 80. b, Thin-walled vascular channels. Surg. No. 12204. Perdrau's method. × 80.

With high magnification (Fig. 60, b) the multiformity of the cells becomes evident, and their nuclei are seen to vary greatly in size, shape, and amount of chromatin. Many multinucleated cells which represent true neoplastic giant cells

(Fig. 60, b) may be found. The amount of cytoplasm surrounding the nuclei varies enormously. Mitotic figures are numerous, and many abnormal types of mitosis are found. This multiformity of the cells becomes still more obvious when such a tumor is impregnated by Cajal's gold-sublimate method. Under these conditions they are seen to vary not only in size but in shape, round, elongated, pear-shaped, and spindle-shaped cells being found; even imperfectly formed star-shaped astrocytes are often seen (Fig. 61).

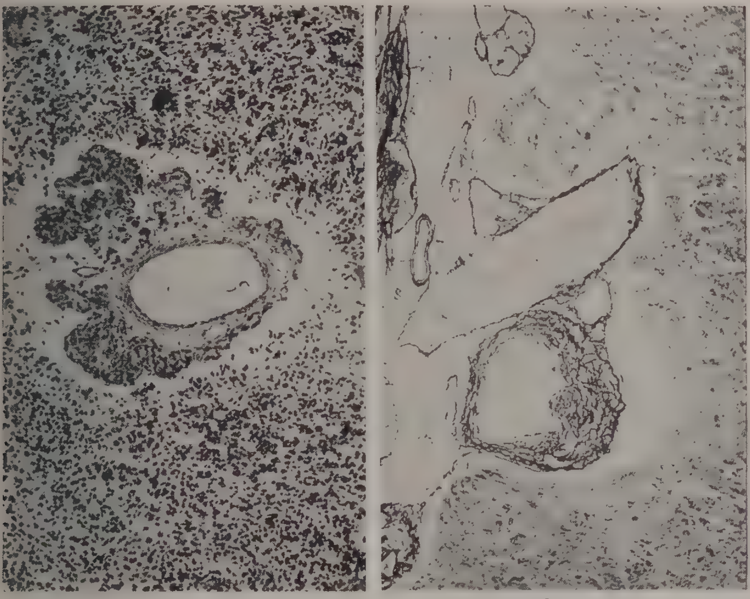


Fig. 64.—Spongioblastoma multiforme. Surg. No. 3351. a, Hematoxylin and eosin. ×80. Overgrowth of vascular adventitia. b, Same formation as seen by Perdrau's method. ×80.

The multiform aspects which such a tumor may present in its various portions are well known, but the study of a number of celloidin sections cut through the entire extent of several tumors has led us to believe that the architectural variation, except in the periphery where the tumor is invading the cerebral tissues, is produced in large part by degenerative changes and the resultant reparative processes. One of the characteristic appearances, due unmistakably to a degenerative process, is shown in Figure 62, a, the central clear area being a necrotic mass surrounded by pyknotic nuclei. When such a degenerative process proceeds somewhat further a peritheliomatous appearance may result, the cells remaining viable only in the neighborhood of the vascular channels (Fig. 63, a). These chance architectural formations must be distinguished from similar ones, due to collections of unipolar spongioblasts (Fig. 62, b), which may be found occasionally in the multiform type of tumor.

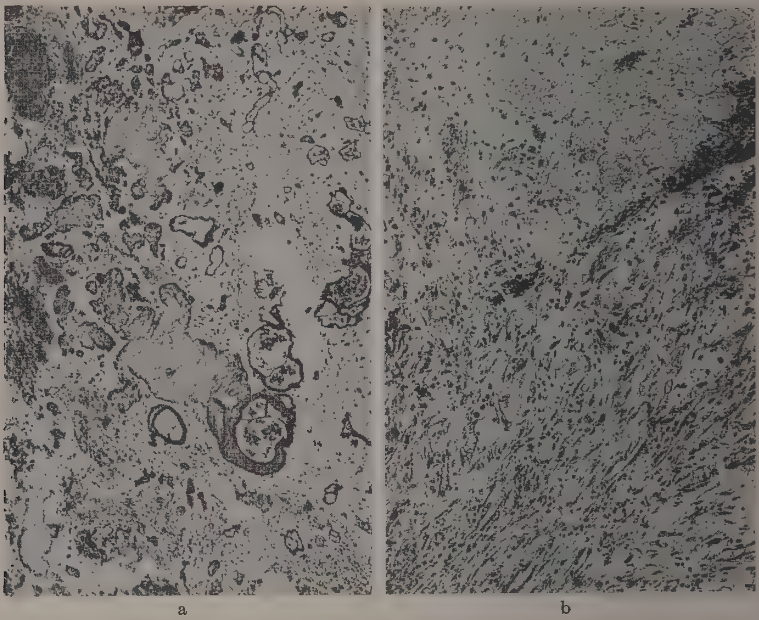


Fig. 65.—Spongioblastoma multiforme. a, Hyalin degeneration of vessel walls. Surg. No. 15530. Perdrau's method. × 80. b, Fibroblasts invading a necrotic area. Surg. No. 242. Hematoxylin and eosin stain. × 80.

The vascular sinuses (Fig. 63, b), which vary greatly in number in different tumors, are usually thin-walled and show many pathological changes, such as overgrowth of the adventitia (Fig. 64, a), under which circumstance the adventitial cells remain sharply demarcated from the surrounding neoplastic tissues (Fig. 64, b). Proliferation of the endothelium and hyaline degeneration of the walls of the vessels also occur (Fig. 65, a) and lead to occlusion of the lumen and necrosis of adjacent areas. The fragile and diseased vascular walls, moreover, are easily ruptured, giving rise to extensive hemorrhages, and into these necrotic and hemorrhagic foci stream fibroblasts which organize and replace the destroyed areas (Fig. 65, b).

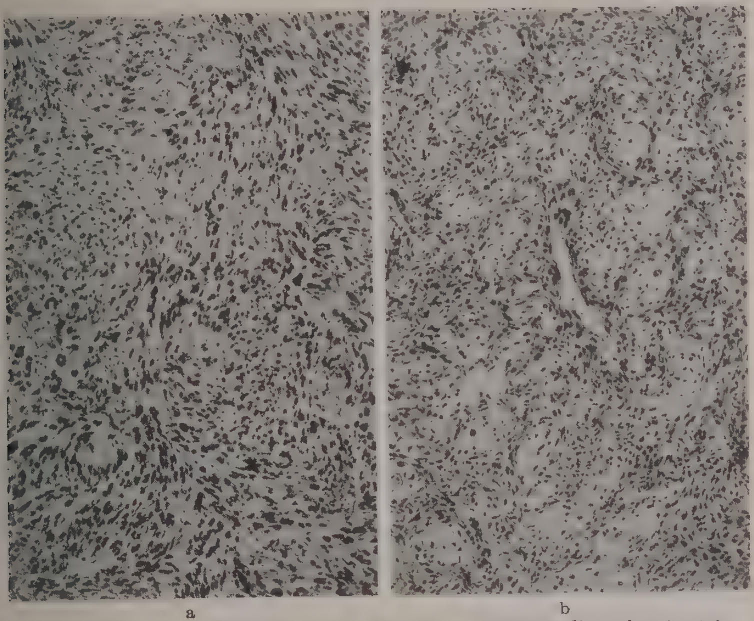


FIG. 66.—Spongioblastoma multiforme. Surg. No. 242. a, Hematoxylin and eosin stain. × 80. Neoplastic tissue near a necrotic area. b, Idem. × 80. Fibroblasts organizing a necrotic area.

Bertrand and Medakowitch [4] have expressed the view that the fibroblasts mingle with the neoplastic cells; also that a metaplasia of fibroblasts into spongioblasts and *vice versa* occurs to form what they call the *"métaplasie du complexe conjonctivo-névroglique."* We have never been able to convince ourselves of the existence of such metaplasia. It is true that the two tissues may bear a close resemblance, but this is only superficial. Thus, Figure 66 shows two areas from the same tumor. The area in Figure 66, a, consists of neoplastic spindle-shaped cells in which signs of degeneration occur, there being a few small vascular channels lined with endothelium quite distinct from the neoplastic cells. The area in 66, b', consists of a necrotic ground substance almost completely replaced by quite healthy spindle-shaped cells which in places form vascular channels, having no other lining than that furnished by the cells themselves. The dividing line between these two types of tissue

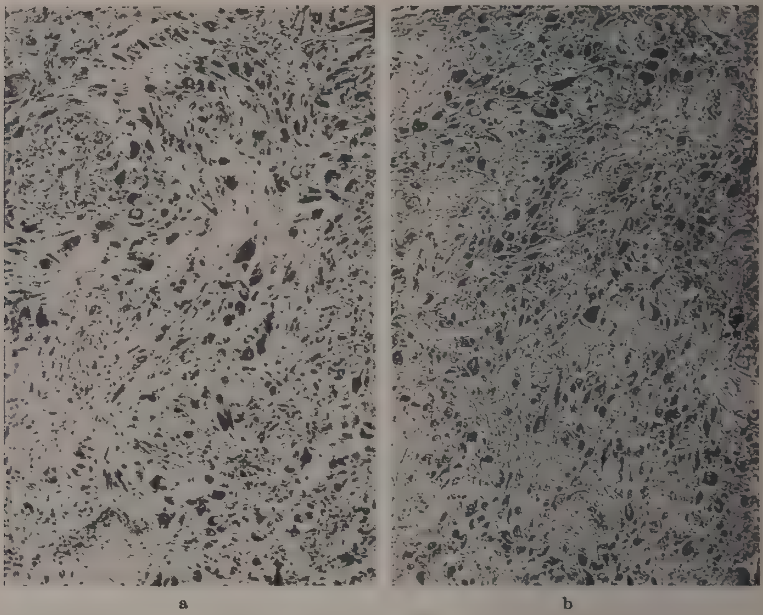

a b

FIG. 67.—Spongioblastoma multiforme. Surg. No. 5570. a, Hematoxylin and eosin stain. ×80. Hyalinization of the neoplastic cells. b, Same stain. ×80. Process more advanced than in "a."

is always sharp, both in this tumor and others, especially when the sections are stained by Perdrau's method.

Other consequences of degenerative changes are deserving of note. The presence of giant cells which result from imperfect cellular division is usually accompanied by a hyaline change of the cytoplasm (Fig. 67, a), a process which may go on to almost complete hyalinization of all the cells in large areas of the tumor (Fig. 67, b). A pseudo-syncytium is sometimes formed, two stages in such a process being shown in Figure 68. Close examination of such areas always reveals hyaline changes, and by Herxheimer's method an increased deposit of fat is shown (Fig. 69, a). The so-called amœboid glioma of Olga Lotmar,[40] the essentially degenerative nature of which is betrayed by

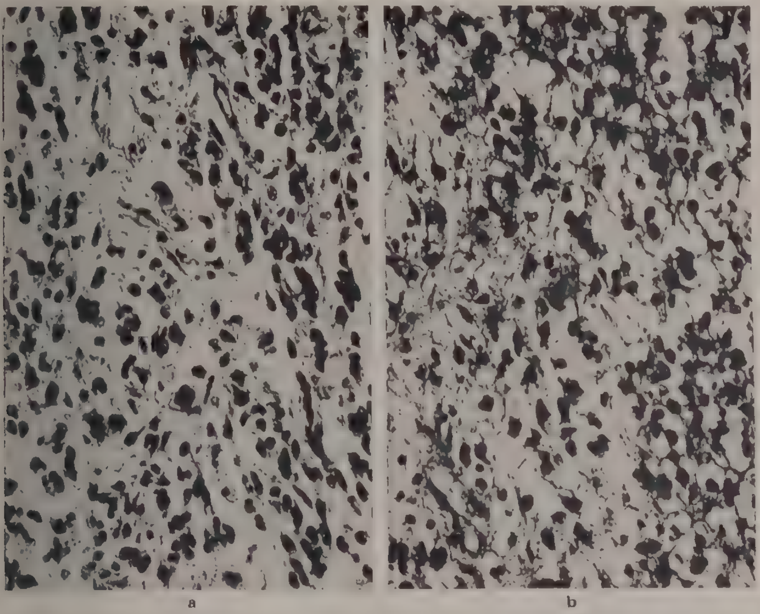


Fig. 68.—Spongioblastoma multiforme. a, Surg. No. 11613. Hematoxylin and eosin stain. × 80. Formation of a syncytium. b, Same stain. × 80. Process more advanced than in "a."

the pyknotic nuclei, the hyalinization of the cytoplasm, the abundance of fat and other *"abbauprodukten,"* in our opinion, is merely due to these changes.

Another common occurrence in these neoplasms, as well as in the protoplasmic astrocytomas to be described, is a sort of liquefaction of the tissue without reparative reaction, resulting in the formation of cysts (Fig. 69, b). Such cysts are usually without an epithelial lining, but, as described by Saxer,[63] certain of them, particularly those which occur in cerebral neoplasms, may possess a sort of pseudo-epithelium formed by the neoplastic cells themselves. The literature concerning these cysts has been collected by Wisbaum[74] and their clinical aspects have been considered in a paper from this clinic by Martin.[43]

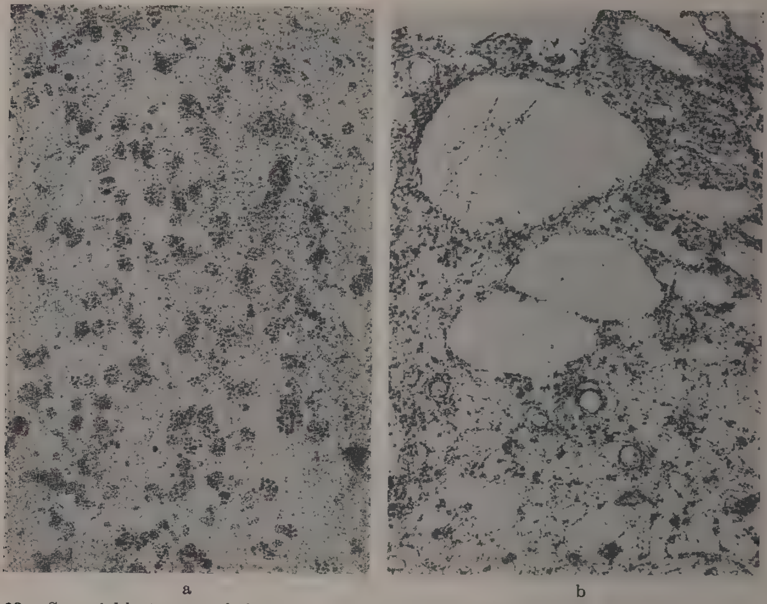


FIG. 69.—Spongioblastoma multiforme. a, Herxheimer's method. × 80. Surg. No. 21120. Fatty degeneration. b, Surg. No. 15. Phosphotungstic acid-hematoxylin stain. × 80. Cystic formation.

Spongioblastomas, furthermore, are diffusely invasive, and as they surround the normal cells of the adjacent cerebral tissues, these also undergo certain degenerative changes in the process of their destruction. A protoplasmic astrocyte which had been thus affected is depicted in Figure 70, a, and the fibrillary astrocyte shown in Figure 70, b, and also the adjacent ganglion cell, have both undergone extensive hyalinization.

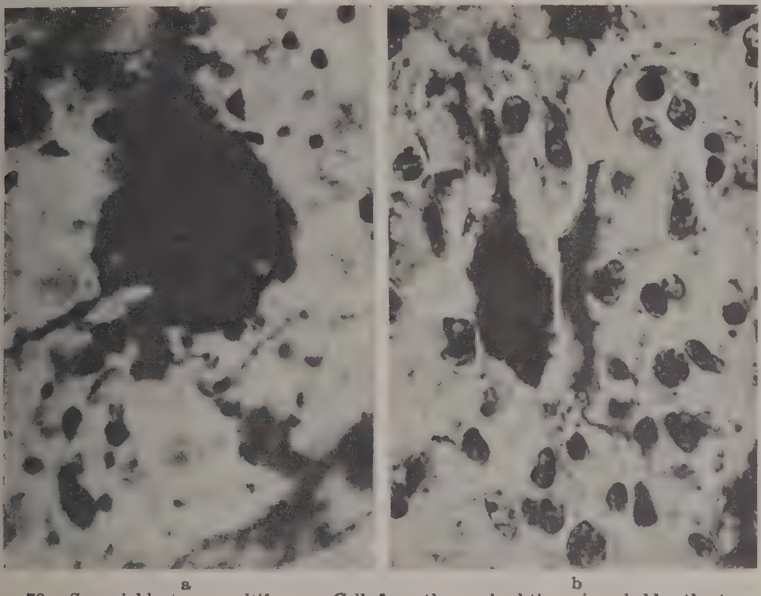


Fig. 70.—Spongioblastoma multiforme. Cells from the cerebral tissue invaded by the tumor. a, Surg. No. 20535. Gold-sublimate method. × 850. Degenerating protoplasmic astrocyte. b, J. H. H. Surg. No. 18512. Phosphotungstic acid-hematoxylin. × 850. Hyalin degeneration of a ganglion cell and of a fibrillary astrocyte.

If we have insisted at undue length upon these degenerative changes it is for three reasons: (1) because the spongioblastoma multiforme is the cerebral neoplasm most often found; (2) because it is especially liable to these changes; and (3) because the multiformity of its structure is largely due, in our opinion, to degenerative and reparative processes.

(b) *Spongioblastoma unipolare.*—A few brain tumors are composed almost wholly of unipolar spongioblasts, with a various proportion of bipolar forms. Under a low magnification they may bear a suggestive resemblance to an acoustic neurinoma (Fig. 71, a). The processes of their cells stain very feebly with phosphotungstic acid-hematoxylin, and appear under the microscope round and hard, like wires. Only where they gather in clumps, as occasionally happens, do they form a striking feature of the microscopic picture. Such clumps may be seen at a higher magnification to be composed of the tails of unipolar cells (Fig. 71, b). Another tumor of this type is shown in Figure 72, with the cells cut longitudinally and transversely. Amitotic division occurs, but mitoses are exceedingly rare.*

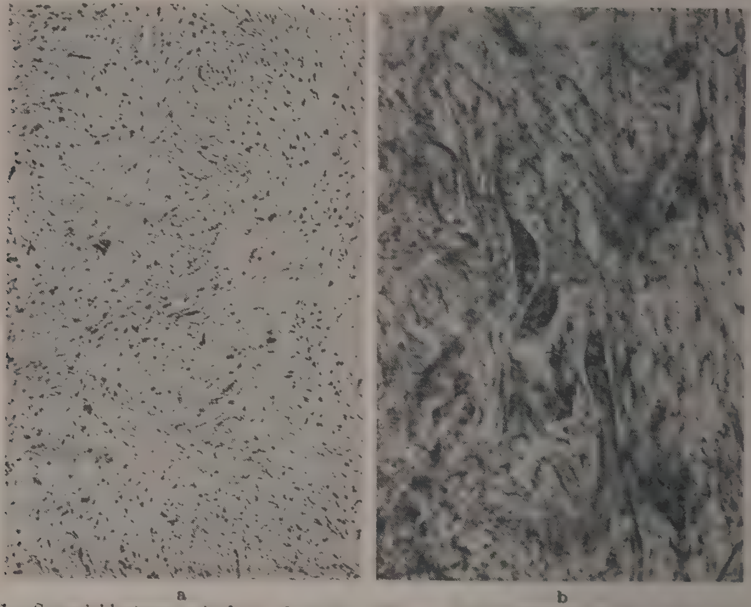


Fig. 71.—Spongioblastoma unipolare. Surg. No. 1963. a, Phosphotungstic acid-hematoxylin. × 80. Note resemblance to acoustic neuroma. b, Same stain. × 850. Tangled mass of unipolar spongioblasts.

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* Josephy,[38a], has recently described a cystic and calcified tumor of the hypothalamus as a "zentralem neurinom." It appears from his histological description to be identical with our spongioblastoma unipolare.

9. Astroblastoma.—Comprising this group are the tumors composed almost wholly of astroblasts. They are quite unmistakable in their microscopic appearance, and show the following characteristics. The structure of the tumor is loose (Fig. 73, a). The cells have considerable cytoplasm, and often possess two or three nuclei. From one pole of the cell a thick process extends to a blood-vessel, on the wall of which it ends in an expansion (Fig. 73, b). From the opposite pole of the cell a few feeble short processes extend in various directions. There are no mitotic figures. No neuroglia-fibrillæ can be demonstrated by phosphotungstic-hematoxylin or other methods. Typical cases are figures by Greenfield[26] under the name of neuroblastoma.

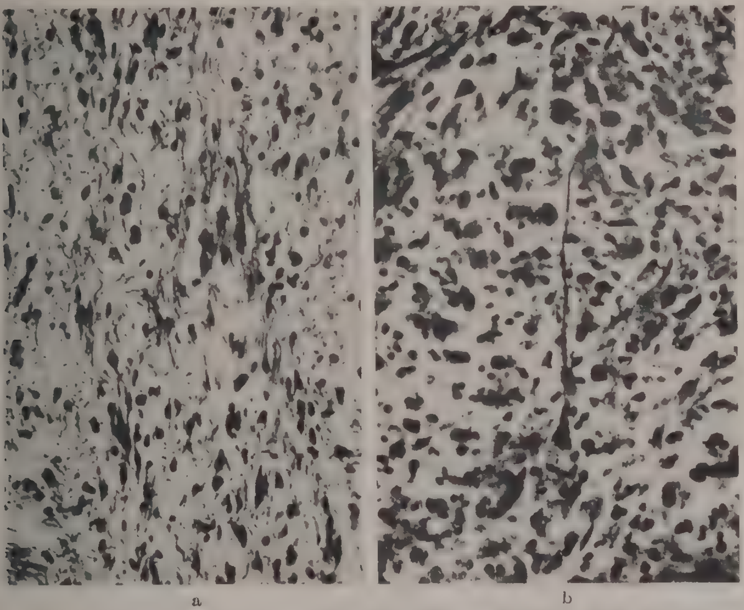


Fig. 72.—Spongioblastoma unipolare. Surg. No. 10231. a, Methylene blue eosin stain. × 300. Unipolar spongioblasts, sectioned longitudinally. b, Achúcarro's tannic silver method. × 300. Same cells sectioned transversely except one which by chance lay in the plane of section.

These neoplasms are often called ganglion-celled gliomas because of the resemblance of the triangular bodies of the cells to those of the cortical neurones. But it is easily shown that the thick process coming from the apex of the triangular cell body is not a dendrite, but ends in a sucker foot on a vascular sinus. Moreover, the cells with all their processes are easily impregnated by the gold-sublimate method of Cajal. They never contain tigroid bodies, and their nuclei bear no resemblance to those of nerve cells.

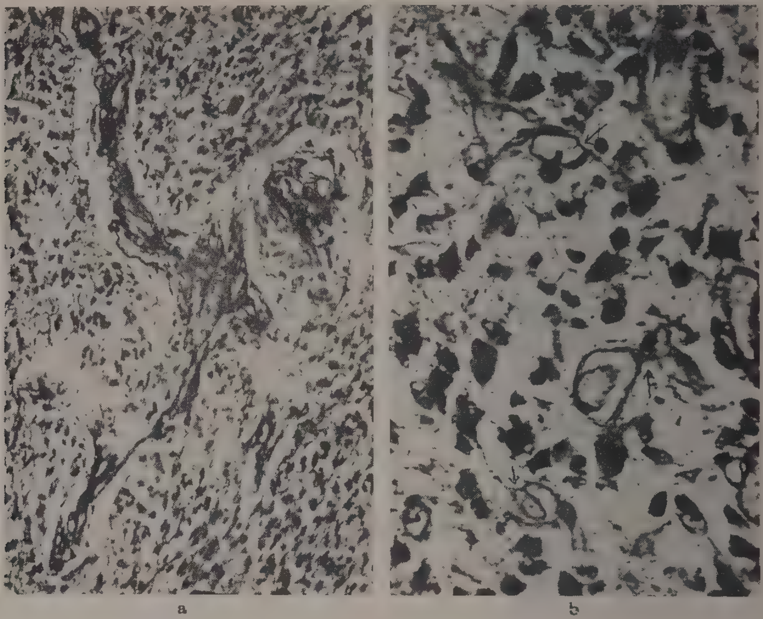


Fig. 73.—Astroblastoma. a, Surg. No. 1114. To show the loose character of the tumor. Phosphotungstic acid-hematoxylin. × 100. b, Surg. No. 6408. Phosphotungstic acid-hematoxylin. × 300. Note the vascular "sucker feet" (arrows).

10. Astrocytoma.—In this class are placed tumors consisting almost wholly of astrocytes, and they may be divided into two distinct types, protoplasmic and fibrillary, between which numerous intermediary forms occur, as they do also between astroblastomas and the protoplasmic astrocytomas.

(a) *The Protoplasmic Type.*—These are soft, relatively avascular tumors often arising from the cerebral or cerebellar cortex, and almost as liable to degenerative and cystic changes as is the spongioblastoma multiforme. They may consist wholly of protoplasmic astrocytes, with only a few small vascular channels (Fig. 74, a). No neuroglial fibrillæ can be demonstrated, but the stellar shape of the cells may be plainly seen when impregnated by Cajal's gold-sublimate method, which shows the whole extent of their branching processes (Fig. 74, b). Amitotic cellular division is common (Fig. 75, a) but mitoses are rarely seen. Many nerve fibres with altered myelin sheaths may be found passing through these soft tumors (Fig. 75, b).

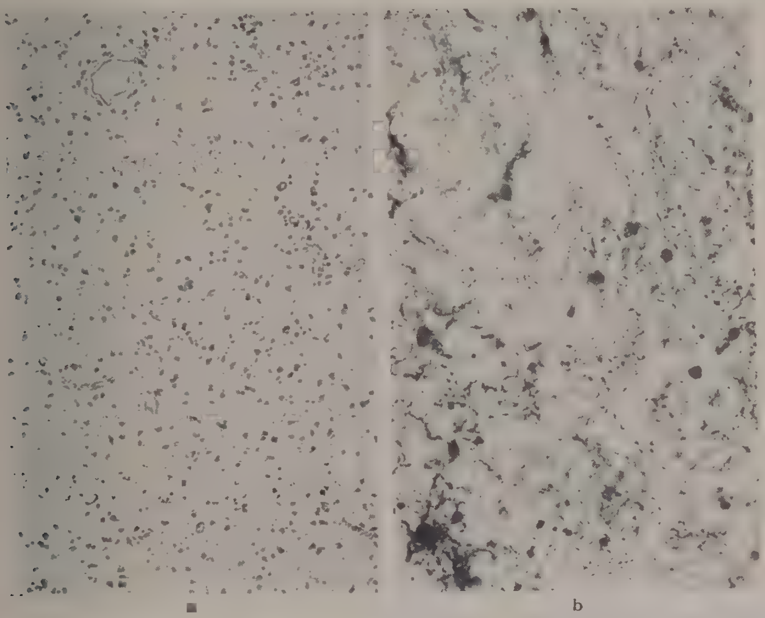


Fig. 74.—Astrocytoma protoplasmaticum. a, Surg. No. 1527. Phosphotungstic acid-hematoxylin stain. × 80. Nuclei are widely scattered and the internuclear material is unstained. b, Surg. No. 19383. To show star-shape of cells. Gold-sublimate method. × 300.

(b) *The Fibrillary Type.*—The term astrocytoma fibrillare is one we prefer to give to a comparatively common lesion composed almost wholly of fibrillary cells, though a small and variable number of protoplasmic astrocytes may be present. The term " astroma " is said to have been proposed for these lesions in an early paper by Lenhossek,[38] who states therein that Golgi, in 1872, was the first to show that it is the astrocyte on which the diagnosis of glioma had been usually made—and still is, for that matter. What is more, the typical glioma made familiar in 1895 by the drawing from Stroebe's [68] paper, so often reproduced, is a tumor composed largely of these cells.

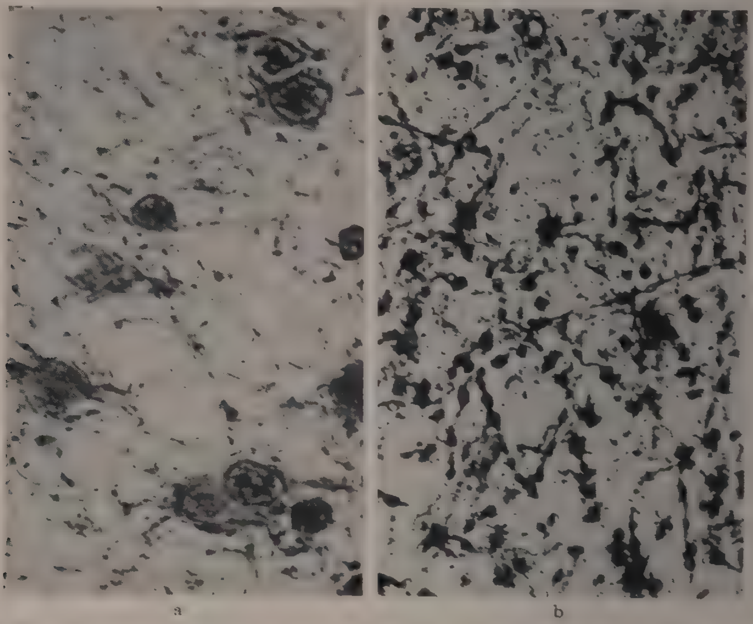


FIG. 75.—Astrocytoma protoplasmaticum. a, Surg. No. 1055. Phosphotungstic acid-hematoxylin. ×850. Amitotic division is shown. b, Surg. No. 20715. Gold-sublimate method. ×300. Many myelin sheaths are seen running through the soft tumor.

The appearance of the tumor under low magnification shows a feltwork of neuroglia-fibrillæ, between which are scattered widely separated nuclei (Fig. 76, a). Mitotic figures are not found and amitotic division is rare. A few small blood-vessels are present (Fig. 76, b), but they are infrequent, and it may be due to this that the tumor is prone to cystic degeneration. The nature of the neoplastic cells is beautifully shown by Cajal's gold-sublimate method (Fig. 77, a). Sometimes calcified plaques may be found, through which run neuroglial fibrillæ (Fig. 77, b).

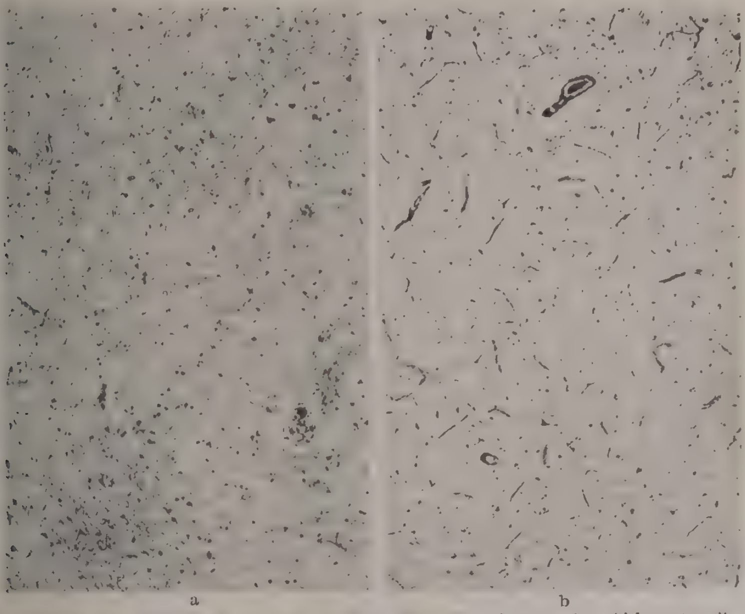


FIG. 76.—Astrocytoma fibrillare. a, Surg. No. 19088. Phosphotungstic acid-hematoxylin. × 80. Nuclei are widely separated by an abundant feltwork of neuroglia-fibrillæ. b, Surg. No. 19823. Perdrau's method. × 80. To show scanty vascularization.

11. OLIGODENDROGLIOMA.—A cellular tumor of peculiar type (Fig. 78, a), in which fibrillary astrocytes occasionally appear, is sometimes encountered. The neoplastic cells have

spherical nuclei with a heavy chromatinic network, and are surrounded by a ring of cytoplasm which stains very feebly by ordinary staining methods. Between the cells is an indefinite material which stains neither for neurofibrillæ, neuroglia, nor for connective tissue (Fig. 78, b). This material may give the growth somewhat the appearance of the cross-section of a plant. No mitotic figures can be found. These tumors are prone to become calcified.

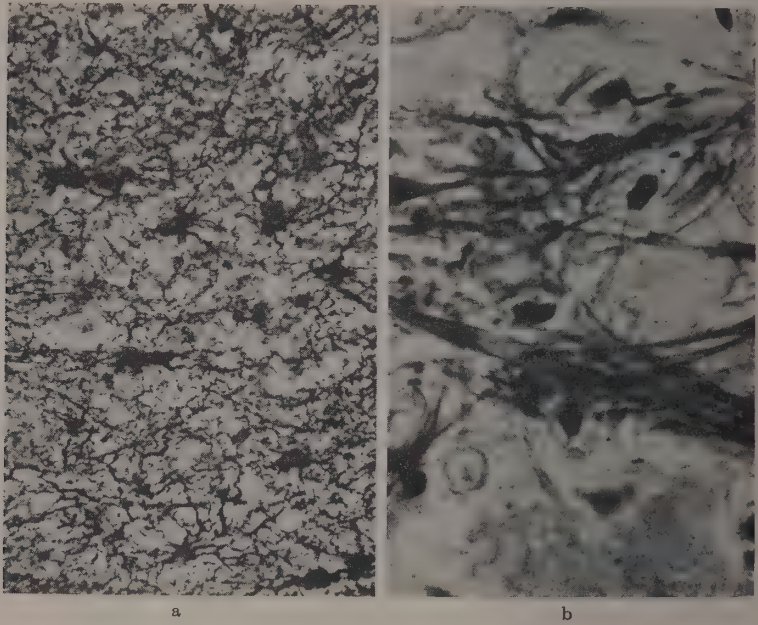


FIG. 77.—Astrocytoma fibrillare. Surg. No. 19823. a, Gold-sublimate method. × 300. To show the character of the neoplastic cells. b, Phosphotungstic acid-hematoxylin stain. × 350. Calcified plaque through which extend fibrillæ.

It seems probable that the cells of these peculiar neoplasms are oligodendroglia, though we have never been fortunate enough to secure a fresh specimen for impregnation with Hortega's specific method for these cells. However, the resemblance of the histological picture is very suggestive with ordinary staining methods, as already shown (*cf.* Fig. 35, a).

It is claimed by Ziveri[77] that the imperfectly developed astrocytes sometimes found in these tumors are merely inclusions of the normal neuroglia. This view does not seem to be exact, since the astrocytes are seen in all stages of differentiation and show no signs of degeneration. Hortega believes that both the oligodendroglia and fibrous neuroglia between the long-fibre tracts arise by differentiation of medulloblasts which have wandered into these positions. By a similar hypothesis the presence of astrocytes in these tumors may be satisfactorily explained.

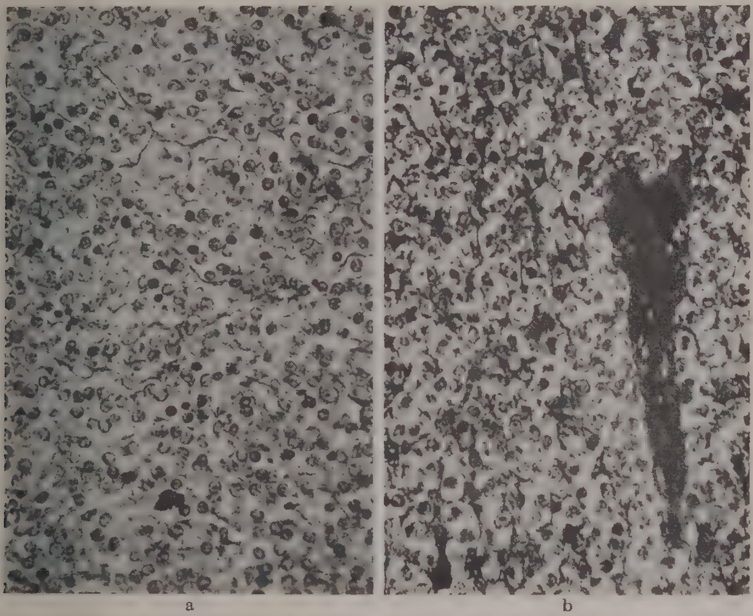


FIG. 78.—Oligodendroglioma. Note the spherical nuclei, unstained cytoplasm and indefinite intercellular material. a, Surg. No. 13924. Aniline blue-orange G. stain. × 300. b, Surg. No. 5490. Hematoxylin and eosin stain. × 300.

12. Neuroblastoma.—The tumor already described under the name of medulloblastoma is often called a neuroblastoma. The term, first applied to a similar tumor of the sympathetic nervous system by Wright, as already explained (page 63), gives an erroneous impression of the true nature of the neoplastic cells. Actual neuroblasts are rarely found in these tumors, the majority of the cells being in an earlier stage of embryonic development, few of them being even potentially neuroblasts.

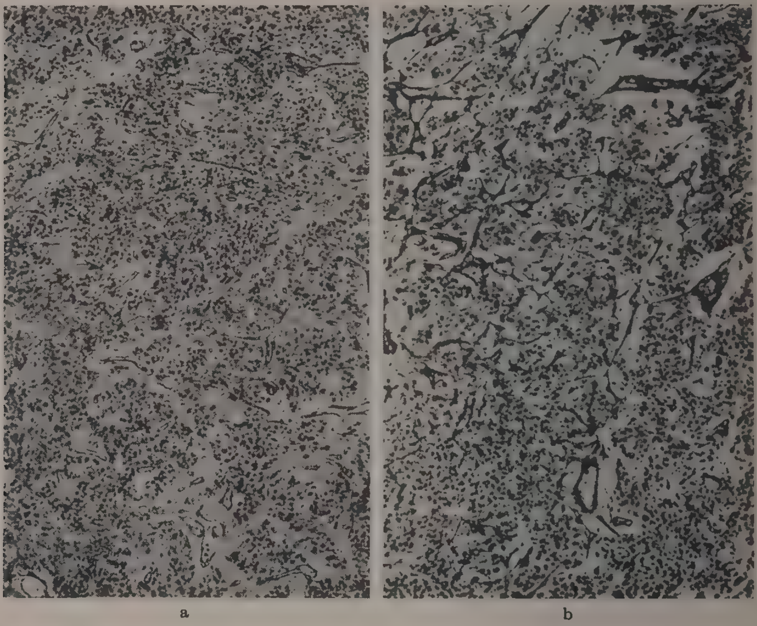


Fig. 79.—Neuroblastoma. Surg. No. 15265. a, Phosphotungstic acid-hematoxylin stain. × 80. To show bands of fibrillary material. b, Hortega's fourth variant. × 80. Note attempt to form connective tissue stroma.

Tumors composed principally of unipolar neuroblasts are exceedingly rare. Only two have been positively identified in this series, though one other similar tumor was found which had not been properly fixed for the employment of specific impregnation methods. Moreover, the two hypothetical apolar neuroblastomas discussed in a previous section (page 43) should possibly be included in this group.

Confining our attention, however, to the two positive cases, we find that they are both quite cellular tumors, very similar in appearance, composed almost wholly of unipolar neuroblasts. Under a low magnification are seen (Fig. 79, a) long streaming bands free from nuclei and filled with fibrillary material which remains unstained by phosphotungstic acid-hematoxylin and by Hortega's fourth variant, but which nevertheless can be shown by Cajal's method to be composed of processes of uni-

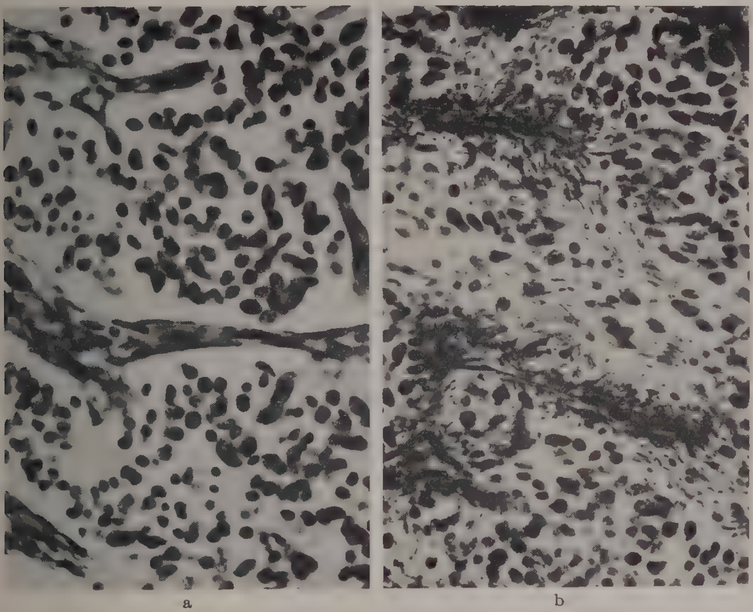


FIG. 80.—Neuroblastoma. Successive sections stained by two methods. Surg. No. 15265. a, × 300. Hortega's fourth variant. No neuroglia stained. b, Cajal's reduced silver method. × 300. Numerous neurofibrils are impregnated.

polar neuroblasts (Fig. 80, b). These processes are unmyelinated and usually end in a bulb near the blood-vessels to which, however, unlike the processes of the astroblasts, they are not attached. The character of the cells on a higher magnification is shown in Figure 81; and in one of these tumors were found the rosettes depicted in Figure 26, a. Numerous small blood-vessels can be shown (Fig. 79, b) to lie in the centre of the bands of fibrillary material; and between them, as pointed out to us by S. B. Wolbach,[77] pass sprouts of connective tissue to constitute a more or less definite stroma.

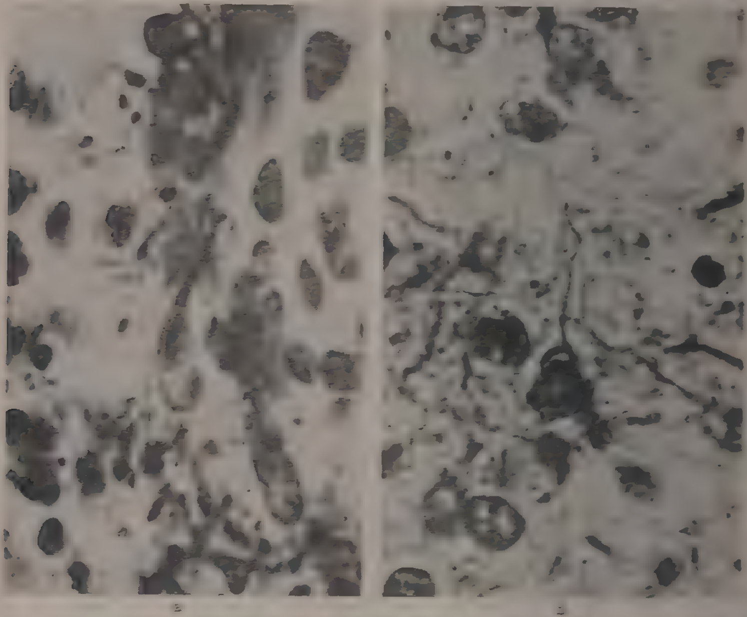


Fig. 81.—Neuroblastoma. Showing unipolar neuroblasts. a, Surg. No. [illegible]. Cajal's reduced silver method. ×550. b, Surg. No. 16313. Cajal's reduced silver method. ×550.

13. Ganglioneuroma.—In addition to a variable amount of glial tissue, either in the form of neurilemmal or neuroglial cells, a ganglioneuroma contains fairly adult nerve cells, which

may or may not be myelinated. No example occurs in the present series, for they are rarely if ever found in the brain, and are with difficulty distinguished from heterotopias. Most of them have been found on the cranial or spinal nerves. Achúcarro [1] and Lhermitte [39] have each described such a tumor in the cerebellum, Pick and Bielschowsky [54] one in the medulla oblongata, Schmincke[66] and Dumas [17] in the cerebrum, and both Greenfield [26] and Robertson [60] have encountered an example in the region of the tuber cinereum, probably arising from misplaced cells of the ganglionic crest.

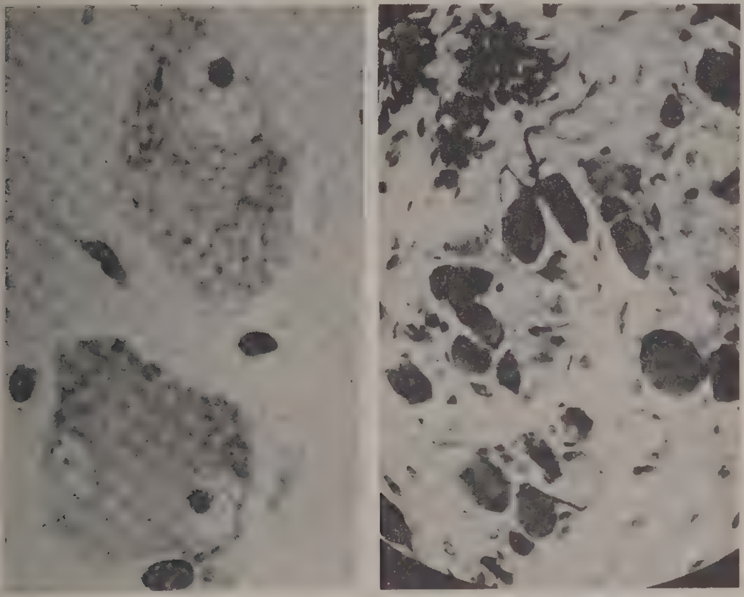

a b

FIG. 82.—Ganglioneuroma. Surg. No. 14560. a, Nissl's method. ×850. Showing Nissl bodies. b, Methylene blue eosin stain. ×300. Abnormal dendritic processes are seen.

The illustrations here given (Figs. 82 and 83) are taken from a tumor which, apparently originating in the intervertebral foramen, grew primarily outside the vertebral column, but afterwards extended inward to press upon the cord. Some of the neoplastic cells show definite Nissl bodies (Fig. 82, a) and nuclei characteristic of nerve cells. Others show processes of considerable length (Fig. 82, b), even though the tissue was fixed in Zenker's fluid so that impregnation methods were precluded. The most interesting feature of the tumor lies in the fact that the greater number of its cells resemble those of a neurinoma, and that all stages of transition between them and the malformed neurones may be seen (Fig. 83, a.) Furthermore, nests of indifferent cells occur in some parts of the tumor. If the tissues could have been properly impregnated, the appearance of the cells would probably have resembled those of a similar tumor reported by Greenfield [26] (Fig. 83, b).

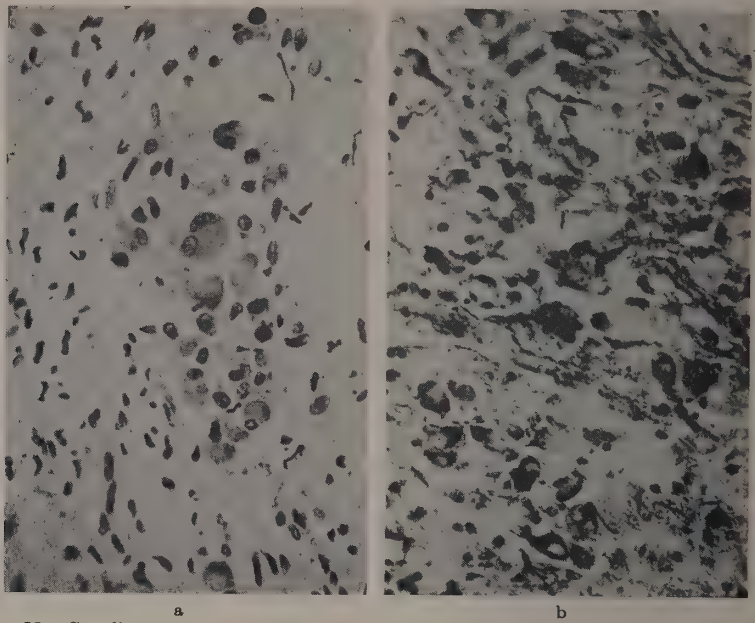


FIG. 83.—Ganglioneuroma. a, Surg. No. 14560. Nissl's method. × 300. Transitions between neuroblasts and neurinoma cells. b, Copied from Greenfield. Intracranial ganglioneuroma. Bielschowsky's method.

14. PAPILLOMA CHORIOIDEUM.—These cases, of which there have been six in the series, have recently been made the subject of a detailed report by Davis and Cushing.[15] They are unmistakable tumors which require no special staining methods for their identification, and they could hardly be mistaken under any circumstances for a glioma. The appearance of such a tumor has already been shown in Figure 43. They are merely included here for the sake of completeness on the basis of their histogenetic origin, which brings them within the group of true tumors of the brain. They need receive no further consideration in the subsequent sections.

NOTE:—In their attempt, throughout this study, to adopt as far as possible the terminology in common use, the authors found themselves obliged to employ certain terms with which they were not wholly satisfied.

Thus in the section on histogenesis (*cf.* pp. 5-9) it would perhaps have been preferable to distinguish more sharply between the primitive spongioblast which is a *bipotential* cell, and the bipolar and unipolar spongioblasts which are *unipotential.* One might well enough reserve the term *spongioblast* for the former, and designate the two latter as bipolar and unipolar glioblasts.

On this basis it would have been possible to avoid the particularly objectionable term neuro-epithelioma and to substitute spongioblastoma for it; one would then employ *glioblastoma* multiforme and unipolare in the place of *spongioblastoma* multiforme and unipolare.

F. ORIGIN OF BRAIN TUMORS

Of all organs of the body, with the possible exception of the uterus, the brain appears to be the most frequent seat of neoplastic disorders. One is consequently impelled to seek an explanation for this phenomenon, and three questions at once propose themselves: (1) Why do certain of the cells suddenly begin to multiply? (2) Which cells begin this process? and (3) Do all of the gliomas have a common cellular origin?

Answers to these questions as yet remain hypothetical, the most generally accepted view being based on the conception of misplaced and retarded embryonic cell groups. And it would seem that nowhere in the body was there a more promising site for the formation of embryonic "rests" in the sense of Cohnheim. The normal differentiation of the cells of the brain is self-regulating and depends on an orderly and simultaneous differentiation of adjacent parts. When it is realized how the cells migrate in the course of their development, the possibility that groups may become isolated and inhibited in their normal growth is readily appreciated. That such groups of undifferentiated cells do occur in the adult brain cannot be doubted, although surely not so often as formerly supposed.

In accordance with the Cohnheim theory, Monakow,[47] Vogt,[72] and others have shown how it is possible at least to explain the malformations of the central nervous system; but whether this applies equally to the development of neoplasms is less clear. However, Bonome[6] has warmly supported this view in the case of the gliomas. He considered as "*cellule gliogenetiche*" certain cells scattered over the brain which were to all appearances undifferentiated, that is to say, cells which seemed to consist of an almost bare nucleus without cytoplasmic processes. These cells, which he called *"cellule indifferente,"* were well known to histologists under various names: as rounded cells (Eisath), preamœboid cells (Rosenthal), cuboid cells (Cerletti), third element (Cajal), etc. They were generally believed by all to be embryonic germinal cells of the nature of Schaper's *"indifferenten zellen,"* to which we have frequently referred.

Unfortunately the recent work of del Río-Hortega has weakened the foundations of this hypothesis. He has shown that among the " cellule indifferente " are many which are far from embryonic, and also that their embryonic appearance was due simply to the inadequacy of ordinary technical procedures to display their rich arborizations. Among these indifferent cells were placed the microglia, the oligodendroglia, and probably many protoplasmic astrocytes as well. These cellular types are spread widely over the central nervous system, and because of their highly differentiated structure it is *a priori* no more probable that they give origin to tumors than that the other cells of the central nervous system should do so. It cannot be denied that the cells comprising the oligodendroglia have a structure almost as simple as that of Schaper's indifferent cells, as is true also of the analogous capsule cells of the sympathetic ganglia. However, as Hortega has emphasized,[36] everything seems to indicate that they are fully developed and highly adapted to their particular functions.

But in addition to these diffusely scattered cells constituting the microglia and oligodendroglia, clusters of cells resembling lymphocytes may occasionally be found near the ependymal lining of the ventricles and in the vicinity of blood-vessels.

These appear actually to represent undifferentiated cells, for some reason arrested in their development, and it is reasonable to suppose that certain types of brain tumors may arise from them. As will be emphasized, tumors (medulloblastomas) wholly composed of such undifferentiated cells are frequently encountered in the cerebellum just over the roof of the fourth ventricle.[3] What is more, Pfleger [53] has shown that in this particular location heterotopic groups of cells can be identified in 75 out of 400 cerebellums, and the coincidence can scarcely be accidental. Why such groups of retarded cells should in one case give rise to a heterotopism, in another to a neoplasm or to lesions which are transitional between heteropias and neoplasms (Ernst [19]) is unknown.

A formal statement of the Cohnheim theory of tumor origin and its relation to heterotopic formations, as given by Ranke [56] and Monakow,[46] adequately accounts for the structure and incidence of some of the mixed tumors which we have described, such as the medulloblastomas, the neuroblastomas, the pinealomas, and the ganglioneuromas. It is not so evident that the same theory necessarily obtains in the case of tumors consisting wholly of cells of the spongioblastic series. We may perhaps invoke for these the theory of Samuel (*cf.* Schaper and Cohen [65]), according to which those cells of least specialized functional differentiation most easily assume neoplastic traits. And we recognize at once that there do not exist in the central nervous system cells similar to those in the rete Malpighii of the skin, for example, which proliferate normally or under slight provocation.

Certainly the cells possessing the least complicated structure in the adult brain are the oligodendroglia. This does not necessarily mean that they are not mature; and we know from the observations of Hortega that after various insults to the central nervous system they remain strangely silent. Nevertheless it has been supposed by Ziveri[77] that they give origin to tumors which bear a histological resemblance to those described above as oligodendroglioma. Their structure is best explained by the hypothesis already referred to (page 89) and which accounts for the anatomical relationships of the normal interstitial cells found between the long fibre tracts of the brain stem. For according to this hypothesis, the fibrous neuroglia and the oligodendroglia take their origin from the same indifferent cells which have wandered into this region, and that both are specialized cells, highly adapted to their function. This view would tend to put the oligodendrogliomas into the group of mixed tumors in accordance with Cohnheim's theory. But there is no evidence whatever that any of the other varieties of glioma, such as the common spongioblastoma multiforme, arise from the oligodendroglia.

It has been shown by Nissl[48] that the protoplasmic astrocytes may divide amitotically, and even by mitosis under certain provocation. In this capacity for cell division we may legitimately seek for the origin of the protoplasmic astrocytomas, which grow slowly and show a preponderance of amitotic cell division. It is possible also that the spongioblastoma multiforme may arise from the protoplasmic astrocytes. For, as will be emphasized, there are several tumors in our series—tumors partially extirpated at successive sessions—which were obviously protoplasmic astrocytomas when first encountered, whereas later on they had assumed the characteristics of a typical spongioblastoma multiforme with numerous mitoses. In each case a dedifferentiation seems to have occurred with a corresponding increase in the rapidity of growth. Tooth[69] has already recorded examples of this transformation which had been observed in the surgically treated cases at the National Hospital in Queen Square.

Another possible source of relatively undifferentiated cells is found in the roof- and floor-plates and in the ependymal lining of the ventricles. It is from such cells that the ependymomas and the medullo-epitheliomas arise, but the view that all gliomata originate in aberrant rests of ependyma, as some authors assert, can hardly be entertained. Nevertheless, to such malformations of the central canal and canaliform evaginations of the ependyma as have been described by Podmaniczy[55] and Guillery,[27] the neuro-epitheliomas and the allied ependymoblastomas can possibly be attributed with some degree of probability.

On the theory of embryonal rests, one can thus account logically for the structure of the medulloblastomas, the neuroblastomas, the pineoblastomas, the pinealomas, the ganglioneuromas, the neuro-epitheliomas, the ependymoblastomas, possibly also for the oligodendrogliomas; whereas the theory of Samuel accounts more or less obviously for the medullo-epitheliomas, the ependymomas, the protoplasmic astrocytomas, and also, of course, for the choroidal papillomas.

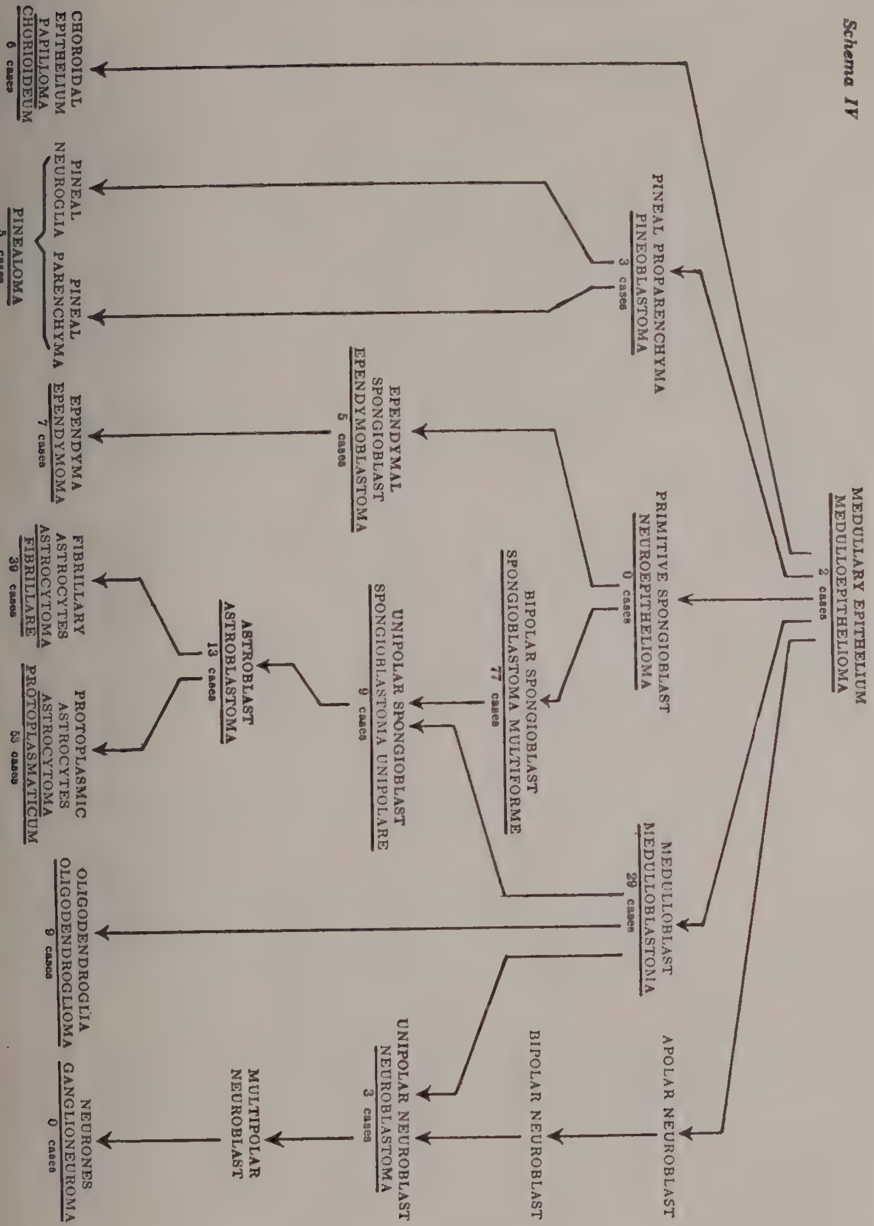
But the origin of the unipolar spongioblastomas, the astroblastomas, and especially of the common spongioblastomas of multiform type is, from lack of evidence, much less logical or obvious, and the very existence of a microglioma may be dismissed as problematical. Moreover, the fibrillary astrocytomas are perhaps not blastomata at all, but of the nature of heterotopia.

The reason for the sudden assumption by these various cells of a continuous and neoplastic growth remains obscure. This is the great defect of the Cohnheim-Ribbert theory, which fails to explain what the influences may be that suddenly arouse into active growth cells which happen to have been misplaced and retarded in their development. Release of tissue tension, increased blood supply, disturbance of organization, are some of the uncertain factors invoked by the theory of cellular autonomy. There is perhaps this to say for the release of tissue tension, that gliomata sometimes appear to grow with increased rapidity after operative interference, or after the mere release of intracranial tension by decompressive operations; but it is difficult clinically to distinguish between actual increase of size and œdema under these circumstances.

As is true of tumors in general, there is often a history of trauma, perhaps more often in brain tumors than in other situations. Moreover, certain pathologists have assumed that some stimulus (*Reiz*), possibly of a chemical nature, must be present. In this connection we may call attention to a fact often brought out in the clinical histories, namely, that pregnancy appears to have an influence in stimulating to activity what up to that time has been a symptomatically quiescent lesion. Even so, when all has been said, the essential cause of neoplastic growth in the brain, as elsewhere, eludes us.

The relationships of these several types of glioma which have been discussed, to one another and to the underlying histogenesis of the brain may be represented by Schema IV, in which they have been superimposed, in accordance with the predominant cellular type possessed by each, upon Schema I. It will be noted that spongioblastoma multiforme is placed on a level with the bipolar spongioblast. This position is given only for convenience, since the cells of the spongioblastoma multiforme probably do not represent the bipolar spongioblast, nor do they reproduce accurately its structure, for, as we have seen, they may arise by dedifferentiation from protoplasmic astrocytes. Nevertheless, the predominant cellular type is a spindle-shaped bipolar one, and the tumor belongs about in this position when judged by its rapidity of growth, which will be further emphasized in the next section.

Schema IV


MEDULLARY EPITHELIUM
MEDULLOEPITHELIOMA
2 cases
PINEAL PROPARENCHYMA
PINEOBLASTOMA
3 cases
PRIMITIVE SPONGIOBLAST
NEUROEPITHELIOMA
0 cases
MEDULLOBLAST
MEDULLOBLASTOMA
29 cases
APOLAR NEUROBLAST
BIPOLAR SPONGIOBLAST
SPONGIOBLASTOMA MULTIFORME
77 cases
BIPOLAR NEUROBLAST
EPENDYMAL
SPONGIOBLAST
EPENDYMOBLASTOMA
5 cases
UNIPOLAR SPONGIOBLAST
SPONGIOBLASTOMA UNIPOLARE
9 cases
UNIPOLAR NEUROBLAST
NEUROBLASTOMA
3 cases
ASTROBLAST
ASTROBLASTOMA
13 cases
MULTIPOLAR
NEUROBLAST
CHOROIDAL
EPITHELIUM
PAPILLOMA
CHORIOIDEUM
6 cases
PINEAL
NEUROGLIA
PINEAL
PARENCHYMA
PINEALOMA
5 cases
EPENDYMA
EPENDYMOMA
7 cases
FIBRILLARY
ASTROCYTES
ASTROCYTOMA
FIBRILLARE
39 cases
PROTOPLASMIC
ASTROCYTES
ASTROCYTOMA
PROTOPLASMATICUM
53 cases
OLIGODENDROGLIA
OLIGODENDROGLIOMA
9 cases
NEURONES
GANGLIONEUROMA
0 cases

G. CLINICAL CORRELATION

WHILE the pathological material was being assembled in accordance with the schema outlined in the previous section, the clinical records of the 414 cases indexed under the caption "glioma" up to January 1, 1924,* were independently abstracted and assembled with special regard to the total length of life for each case from the date of onset of symptoms. For it remained to be seen whether the classification so laboriously evolved might have any significance for the clinic so far as operability and prognosis were concerned.

Experience had already taught us that the diagnosis of "glioma" did not necessarily carry with it an ultimately hopeless prognosis; but we were at a loss to know how it could be that a patient, from whose cerebellum a large tumor diagnosed "glioma" was removed as long ago as 1906, might prove to be living and well, the father of a family, and a wage-earner 19 years later, whereas another patient from whom a "glioma" happened to be removed in like fashion, supposedly in its totality, might survive for a scant six months before a rapid recurrence took place. So, too, in the case of the gliomatous cysts; how could it be that one patient might have but temporary relief after the evacuation of a large cyst, whereas another might remain well for twenty years and then present himself, because of a return of symptoms, to have at this late day a tumor nodule, pronounced "glioma," removed from the situation of his former cyst? These were questions for which we needed an answer—

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* This date was fixed upon so that a year or more might have elapsed after operative verification in order to get the final end results of the more rapidly growing tumors.

questions of vital importance to all concerned: to the attending physician and the surgeon no less than to the patient and his family. They were questions, moreover, which could only be answered by clinical records covering a long period of years, and it is for this reason that the early Johns Hopkins cases in the series have come to be of so great importance.

It was inevitable that many pitfalls should beset such a statistical study as we had undertaken, and 104 of the 414 tumors have come to be excluded for the following reasons: in 48 of them a gliomatous lesion had been " verified " merely by the collection from a subcortical cyst of characteristic yellow clotting fluid,* rather than by a histological study, which should be the true criterion; 56 other cases were discarded since a proper differential examination could not be made, either because the material removed at operation did not suffice for a thorough study, or because the lesion was merely identified as " gliomatous " from slides forwarded to us, stained by methods which did not permit of differentiation. Of the remaining 308 cases in which a proper histological reëxamination of the tissues was possible, 11 gliomas of the optic chiasm † and 18 tumors of pons and midbrain were set aside as unclassifiable, since the histogenesis of the interstitial tissues of these regions is too imperfectly known to allow a proper evaluation of their tumors. Five other cases were discarded, as restudy convinces us they do not belong in the glioma series at all, but in reality are tumors of the cerebral blood-vessels (peritheliomas), which will be reported at another time and place. An additional 22 cases, which represent atypical or transitional forms difficult to classify properly, have also been excluded.*

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* The lesion in many of these cases will doubtless in time be histologically verified, for patients may go many years after the evacuation particularly of a large cerebellar and subcortical cyst before there is a return of symptoms, when, at a second or even a third or fourth operation, the mural tumor may be removed and verified. As the astrocytomas are particularly prone to undergo these cystic transformations, " gliomatous cysts " in the long run have a relatively favorable prognosis; as have also those gliomas in which calcareous deposits occur. The presence of yellow clotting fluid is not necessarily conclusive evidence that a gloma is the basis of the lesion, for similar fluid may be found in the cystic peritheliomas, but these are so relatively rare compared to gliomas that they may be disregarded in one's calculations.

† These cases have been made the subject of a special report from this clinic.[44]

Thus, for one reason or another, we have felt obliged to eliminate over a third of the recorded cases, but there remains a number quite sufficient for the purposes of our present study. The list can be conveniently tabulated as follows:

TABLE III. THE 412 GLIOMAS, UNCLASSIFIED AND CLASSIFIED.

A. Verified by cystic fluid alone		48
B. Excluded because differential study impossible		56
C. Unclassified gliomas of optic chiasm, pons, or midbrain		29
Optic chiasm	11	
Brain stem	18	
D. Excluded for other reasons		27
Blood-vessel tumors	5	
Atypical gliomas	17	
Transitional forms	5	
E. Classified		254
1. Medullo-epithelioma	2	
2. Neuro-epithelioma	0	
3. Medulloblastoma	29	
4. Pineoblastoma	3	
5. Pinealoma	5	
6. Ependymoblastoma	5	
7. Ependymoma	7	
8. Spongioblastoma.		
a. multiforme	77	
b. unipolare	9	
9. Neuroblastoma	3	
10. Astroblastoma	13	

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* These lesions deserve and will receive further study. Many of them represent slow-growing gliomas with a long survival period. Two of them have been briefly discussed in an earlier section (pages 43 and 49), one as a possible unipolar neuroblastoma, the other as a possible microglioma.

TABLE III. THE 412 GLIOMAS, UNCLASSIFIED AND CLASSIFIED. (Continued.)

11. Astrocytoma		
a. protoplasmaticum	53	
b. fibrillare	39	
12. Oligodendroglioma	9	
13. Ganglioneuroma	0	
Total		414
Double tumors *		2
Net total		412

It is with the 254 classified tumors that we may now proceed to deal, and a glance at the above table shows that approximately four out of every five fall in the three major groups: 29 medulloblastomas; 86 spongioblastomas, and 92 astrocytomas (207 in all). We might possibly do well to limit our discussion of the expectation of life to these three major groups, for the number of cases representing the other types is too small to justify the laying of any special emphasis upon averages, which may be unduly affected by the inclusion of one or two exceptional examples.

We indeed cannot belittle the inherent difficulties of a critical analysis of these definitely classified tumors from the standpoint of prognosis even in the larger groups. The life period of a tumor may depend more upon its situation than upon its size or rapidity of growth. A small relatively benign tumor may cause early death from blockage of cerebrospinal fluid, whereas a rapidly growing lesion in a silent area of the hemisphere may have a much longer life. Moreover, the enlargement of the intracranial space from separation of the sutures which takes place in childhood favors the prolongation of life in

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* Occasionally a true brain tumor may be found in association with a meningioma, but it is rare for there to be more than one tumor of the glioma series in the same brain. These two examples were: (1) a pinealoma and a glioma of the optic chiasm; (2) a pinealoma and a medullo-epithelioma.

the case of tumors in young people. Then, too, there is a large margin of error in taking the first recorded symptoms as evidence of the onset of the disease, and this error becomes negligible only when the situation of the various types of tumors is essentially the same and the number of cases sufficiently large to eliminate in great measure the unusual ones. It must also be recalled that these tumors occur in a surgical clinic, and the lengthening of the life of many patients and shortening it of others as a result of operation must not be disregarded, though in the long run these two sources of error perhaps tend to correct themselves. Furthermore, of late years many of the tumors have been subjected to therapeutic radiation, which may or may not have lengthened their survival period.

Some of the difficulties just mentioned will be discussed later on, but for the moment, and leaving all else out of consideration, it became immediately apparent, when our two independently made lists were completed and combined, that the

TABLE IV. SHOWING THE AVERAGE SURVIVAL PERIOD FOR THE TUMORS OF DIFFERENT HISTOLOGICAL TYPES.

L = average survival in months from onset of localizing symptoms.
P = average survival in months from onset of pressure symptoms.
E = average survival in months from earliest known symptoms.
A = average of L, P, and E.

	L	*P*	*E*	*A*
1. Medullo-epithelioma	9	5	10	8
2. Pineoblastoma	?	12	12	12
3. Spongioblastoma multiforme	12	10	13	12
4. Medulloblastoma	15	18	19	17
5. Pinealoma	20	13	22	18
6. Ependymoblastoma	25	15	17	19
7. Neuroblastoma	30	21	24	25
8. Astroblastoma	20+	33+	32+	28+
9. Ependymoma	27+	32+	36+	32+
10. Spongioblastoma unipolare	48+	45+	45+	46+
11. Oligodendroglioma	82+	42+	75+	66+
12. Astrocytoma protoplasmaticum	75+	58+	67+	67+
13. Astrocytoma fibrillare	87+	81+	89+	86+

cases with the longest survival period were among the more highly differentiated tumors placed at the bottom of Schema IV, whereas the more rapidly progressing ones were represented by the less differentiated cases which come near the top. This is shown in the accompanying table of general averages, arranged in order of increasing survival periods (*cf.* Table IV).

Since it would hardly be possible to include the full tables of figures from which these calculations were made, it has seemed best to us to limit further discussion to a brief statement of the behavioristic features of the tumors of these various groups, mainly from the point of view of prognosis.

1. THE MEDULLO-EPITHELIOMAS.—As mentioned in an earlier section, we have identified only two lesions of this type. Both were rapidly growing, as evidenced by unusually numerous mitoses; both were in a most unfavorable situation from the point of view of long survival if left to run their course; and both were quite inaccessible to surgery even had an exact localizing diagnosis been possible. It is not surprising, therefore, that the average survival period should have been the lowest in the series, even though the number of cases is too few to justify any undue emphasis upon the fact.

One of the patients was a woman of 48, who was six weeks on the medical service with symptoms suggesting encephalitis lethargica until the development of a choked disc and nystagmus aroused the suspicion of a cerebellar tumor. A suboccipital exploration failed to disclose a lesion, and death occurred six hours later from interstitial hemorrhage into a large tumor of the midbrain (Fig. 84). This was nine months from the first onset of symptoms.

The other was one of the cases with double tumor. A boy of 17 had been under observation on the medical service as a case of diabetes insipidus with ++ Wassermann reaction.

He ultimately developed headaches and showed oculomotor paralyses, but there was never any choked disc. He became greatly emaciated and died on the surgical service without operation thirteen months after the first onset of symptoms. The autopsy revealed a huge medullo-epithelioma of the third ventricle, and independent of this a small pinealoma * which of itself would hardly have given symptoms.

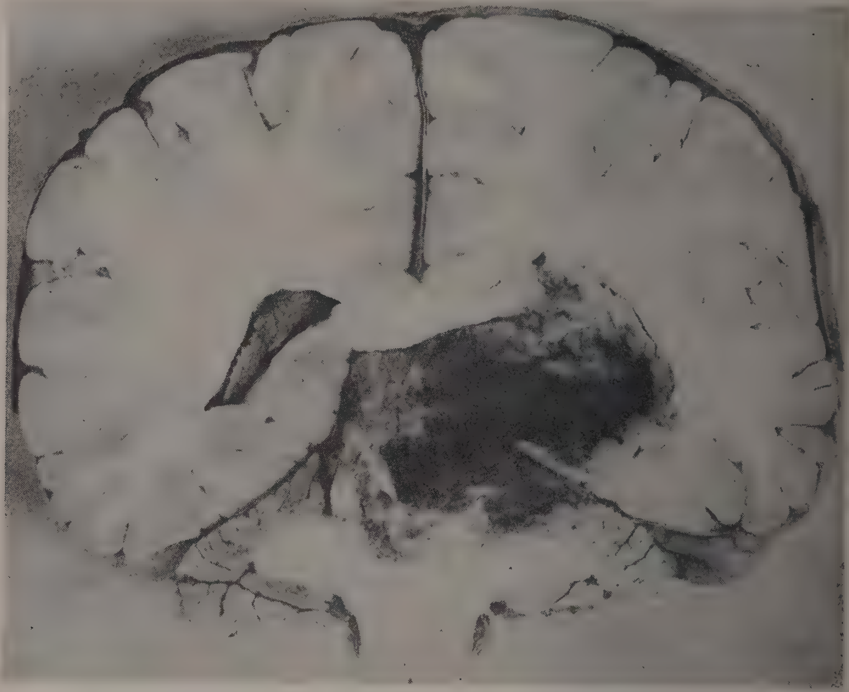

FIG. 84.—Medullo-epithelioma (Surg. No. 17041). Post-operative fatality after a negative suboccipital exploration for a supposed cerebellar tumor. (Four-fifths natural size.)

2. THE PINEOBLASTOMAS.—As already stated, the clinical and pathological aspects of these tumors have recently received a critical analysis in a fully illustrated paper from this clinic by

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* *Cf.* Horrax and Bailey, Tumors of the Pineal Body, *loc. cit.*, Case IX.

Horrax and Bailey. The tumors of both types, pineoblastomas and pinealomas, were therein considered together, for on clinical grounds there is no apparent possibility of distinguishing a pineal growth of spongioblastic from another of a more mature cellular type. The former are more rare, only three cases having now been accepted as such in the series to January 1, 1924, though the later records contain a further example. They are tumors of young people, the average age of the patients being 15 years.

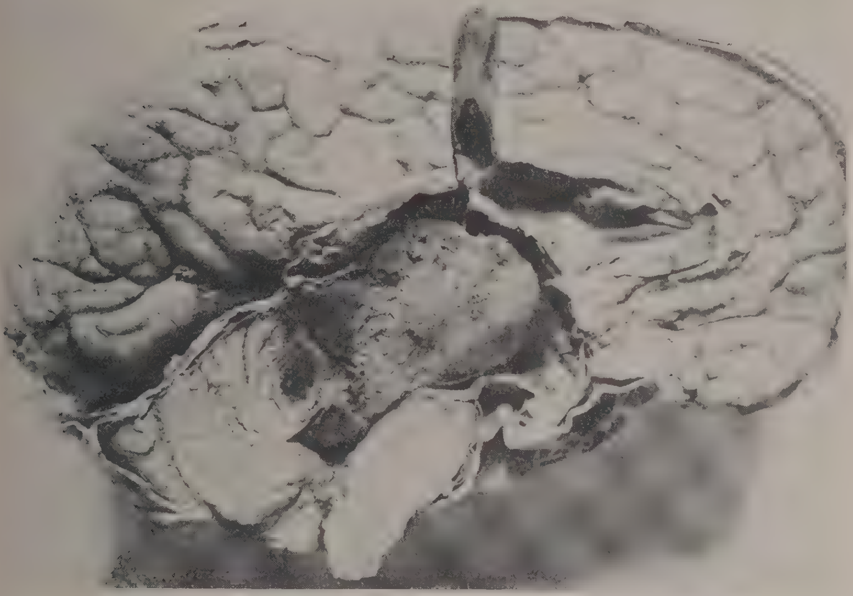

Fig. 85.—Pineoblastoma (J. H. H. Surg. No. 29228), from a child of six with six months' premonitory symptoms suggesting hydrocephalus from a cerebellar lesion. An emergency operation Feb. 12, 1912, because of convulsions and unconsciousness led to ventricular puncture and cerebellar decompression with fatality four hours later from interstitial hemorrhage into the tumor. (Three-fifths natural size.)

In all three cases a tumor of the posterior fossa was suspected because the cerebellar symptoms were sufficiently outspoken to mask the more accurate localization which relative deafness and limitation of conjugate upward movements of the eyes might have suggested. Naturally a tumor was not disclosed in any of these explorations, all of which led to postoperative fatalities. This in one case was due to hyperthermia, and apparently in the others to interstitial hemorrhage into the tumors (Fig. 85), seemingly due to the shift in position of the lesion caused by the suboccipital decompression.

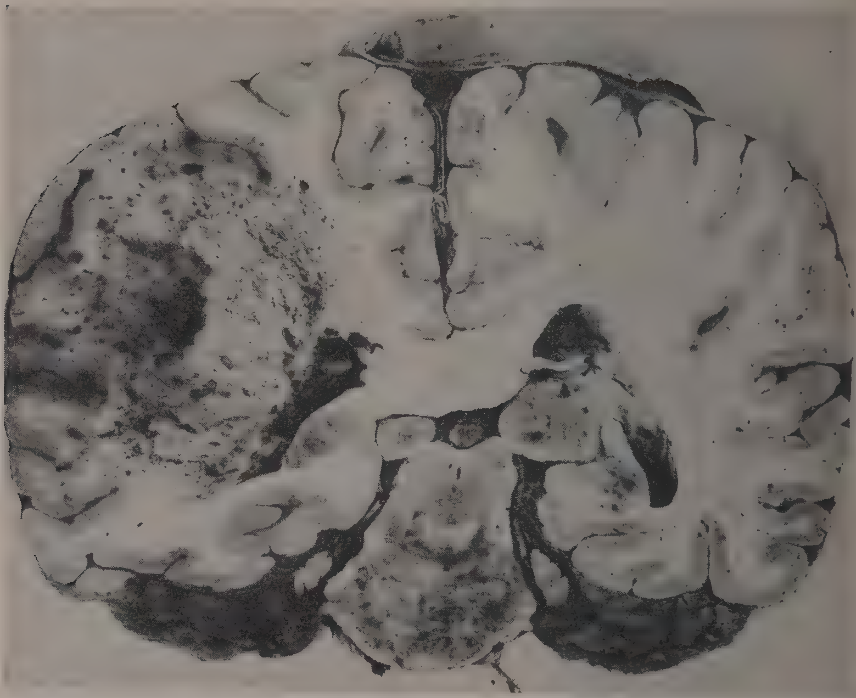

Fig. 86.—Gross appearance of a spongioblastoma multiforme (Surg. No. 15808) in left hemisphere of a patient aged 43 brought to hospital in coma after three months' symptoms mistaken for encephalitis lethargica. After a hypertonic saline infusion a right subtemporal decompression was performed without avail. Death four days after admission. (Four-fifths natural size.)

The reason for considering the two types of pineal gliomas separately in our classification is because they show a different histological structure, the pineoblastoma being obviously a less differentiated and more actively growing lesion. This is supported by the disclosure that the average survival period for the pineoblastomas was six months shorter than for the pinealomas, though this may well enough be attributed to the futile surgical procedures undertaken in these cases, which hastened death.

3. Spongioblastoma Multiforme.*—It is from this group doubtless that the generally unfavorable impression regarding the gliomas as a whole has been gained. It is not only the largest single group in the series, representing about one-third of all the classified cases, but at the same time is one of the most malignant. These are the tumors which usually recur soon after surgical removal, even after extensive removal of the involved area of the brain *en bloc*. The lesion has infiltrating propensities, and from its behavior it is natural that it should have been looked upon as a " gliosarcoma," and have been so designated in former days. When first exposed, the tumor may sometimes have the misleading appearance of enucleability, but when enucleation is attempted, the growth is found at the depth to spread into and merge with the normal cerebral tissue without recognizable demarcation. The appearance of one of these tumors *in situ* unaffected by operative procedure is shown in Figure 86.

These spongioblastomas for the most part are tumors of middle life. The average age of the patients on admission was 41 years; the youngest, 12; the oldest, 69. By decades the cases run as follows: second, 4; third, 11; fourth, 15; fifth, 27; sixth, 14; and seventh, 6 cases. They are therefore predominantly represented in the fifth decade.

They almost invariably occur in the cerebral hemispheres, only two out of the 77 cases having been found in the cerebellum. They consequently are less apt to cause serious complications from cerebrospinal fluid stasis and hydrocephalus than many other tumors less malignant, paralyses and ultimate death being occasioned largely from their bulk alone or in association with cerebral œdema. They do not form metastases, and rarely if ever inoculate the leptomeninges, as do the tumors of the next group to be considered; but they spread widely from the point of origin and, given room, may attain an enormous size. They, moreover, are the only gliomas in the series which have been known to invade the extracranial tissues when the lesion lies subjacent to them after a decompression. The growth in one case even extended down into the patient's neck, behaving much as would a sarcoma; but such a thing is very unusual.

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* These are the tumors described as spongioblastomas by Globus and Strauss,[24] at a meeting of the American Neurological Association in June, 1924. The designation *S. multiforme* was added at our request to distinguish them from the form of spongioblastoma we then described, but have since preferred to call medulloblastoma (p. 118).

Operative precedures, howsoever radical (block extirpations repeated on signs of recurrence; saturation with the X-rays or radium emanations after wide decompression with or without surgical interference with the tumor), have apparently done little more than to prolong life, save vision, and alleviate headache for an average of a few months. First and last there naturally have been many post-operative fatalities in this series. All but five of the cases were operated upon one or more times. In the five unoperated cases, the average duration of life from the onset of symptoms was only three months, which speaks well on the whole for the average survival period of twelve months for those surgically treated.

Only 5 out of the 77 cases had a survival period of over three years from the onset of symptoms. The following brief abstracts of these cases show that they were all ones with premonitory focal epilepsy.

The first of them (Surg. No. 65) was a young man of 22, who originally came under observation in April, 1913. In August of 1910, he had had his initial convulsive attack. A negative cranial exploration had been made elsewhere in November, 1911. The attacks continued and he gradually lost the use of his left side. There were no pressure signs. Operation revealed a large gliomatous cyst with mural tumor, and a total enucleation was attempted (Fig. 87). He did well for nearly two years, when a secondary mass extirpation was necessitated in January, 1915, owing to recurrence of symptoms. The tumor was then a solid glioma, showing increased malignancy. The brain was not radiated. He died three months later. Total duration, four years and eight months; survival from time of primary operation, three years and five months.

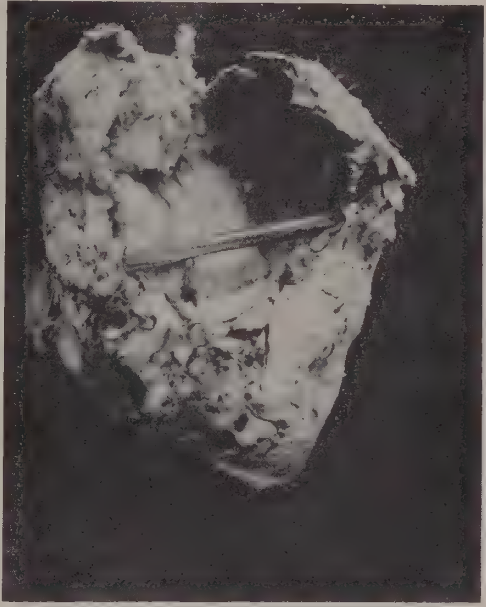

FIG. 87.—A cystic spongioblastoma multiforme (Surg. No. 65) after enucleation. (Natural size.)

The second case (Surg. No. 270): a man of 52 had received a cranial trauma twenty years before entrance, resulting in a partial right hemiparesis, with subsequent spasmodic disturbance of the arm, long regarded as a "writer's cramp." For two and a half years this condition had been recognized as a focal epilepsy involving the arm and leg with a gradually increasing right-sided palsy. There had never been any pressure symptoms. He was operated upon on July 21, 1913, when a small subcortical gliomatous cyst was evacuated. He was readmitted four months later owing to an increase of symptoms accompanied by headaches and a choked disc. At this time a glioma was found and in large part removed. It proved to be a malignant type of spongioblastoma and early recurrence led to his death on March 1, 1914. If the story is to be relied upon, this was nearly twenty years from his original post-traumatic disturbances, about three years from the onset of his palsy, and eight months after his first operation.

The third case (Surg. No. 3774): a married woman of 28 entered the hospital in October, 1915, with the history of uncinate seizures for the preceding twelve months. She had a left homonymous field defect, and at operation a large gliomatous mass was removed from the right temporal lobe. She remained practically free from symptoms for three years. In September, 1918, she reëntered the hospital for a carcinoma of the right breast, and was submitted to a radical operation for this trouble. A recurrence of the glioma led to a second massive extirpation in March, 1919, with temporary relief. She died 14 months later. The tumor at this second session was histologically more malignant in character than before. The whole story therefore covers approximately six years, one before and five after operation.

The fourth example (Surg. No. 3908) was that of a man of 33, who had been having Jacksonian attacks in his right side for five years. Pressure symptoms then supervened, which led to his admission in November, 1915, when a *circa* 100-gram tumor was removed from his left precentral region. It was slightly adherent to the dura, and when first exposed was thought to be benign and enucleable, but no demarcation was found at the depth. The bone flap was removed; he had four deep X-ray treatments (one of the early cases); was free from symptoms for about a year, and died of a recurrence in 18 months without autopsy.

The last example represents possibly our most energetic attempt to prolong the life of a patient with one of these malignant tumors, though had we at the time known just what we were dealing with, we might have been less inclined to persist in our efforts.

A physician's wife (Surg. No. 5440), aged 42, entered the hospital in September, 1916, complaining of headaches of six weeks' duration. In 1909 she had had three general convulsions, and since then innumerable attacks of petit mal, associated with headaches, tinnitus, and a transient numbness of her right hand. On admission there were no objective findings aside from a choked disc of 3 D. A right subtemporal decompression was performed.

She was readmitted three months later because of increasing numbness and disability of the right hand and arm. An osteoplastic exploration on December 18th disclosed a large apparently enucleable tumor slightly adherent to the dura, and, because of the long-standing history, regarded as a probable meningioma. The growth lay in the region of the supramarginal gyrus and was removed, supposedly in its entirety. The operation caused a transient aphasia; from this she completely recovered, though her focal attacks persisted. The tumor was regarded by one pathologist as an endothelioma, by another as a neuroblastoma.

A year later, in August, 1918, owing to her continued attacks, she consulted Dr. W. E. Dandy, in Baltimore, who operated and found a diffusely infiltrating glioma considered to be inoperable. She was subsequently given a number of radium treatments. In May of 1919, she reported again at the Brigham Hospital, and was found in excellent condition, with no evidence of tension and her decompression quite flat.

She reëntered the hospital in October, 1920, owing to increasing aphasia and weakness in the right arm, with complete astereognosis. The flap was reflected for the third time and a massive cystic glioma was removed. There was marked improvement, with relief of all pressure symptoms; and, to a surprising degree, she regained function in her involved arm, even the ability to write.

Five months later symptoms had again returned, and at her husband's insistence, on March 28, 1921, she was again operated upon, a mass of solid tumor being again removed. It showed histologically a lesion of increasing malignancy. She once more made a rapid recovery, with great improvement in all respects. She led an active life until a few weeks before her death, October 5, 1921.

In this case, therefore, seven years of preliminary focal attacks preceded the onset of pressure symptoms; and for nearly five years after her first operation, in spite of the unfavorable situation of the lesion, she managed her household affairs and passed a happy and useful life free from discomforts and with normal vision retained to the end.

More in accord with the great malignancy of these tumors and their ultimately bad prognosis is the fact that only one of the 77 patients up to January, 1924, is still living 29 months after his operation. This unusual result may possibly be ascribed to persistent radiotherapy, for the tumor showed abundant mitoses. The story follows:

The patient, a physician (Surg. No. 17165), aged 44, had an unaccountable attack of transient aphasia in August, 1915, which left him with some hesitancy of expression (both in speech and writing) whenever he became overtired. In June, 1922, he had his first headaches. They were associated with increased difficulty in speech, and in August a choked disc was discovered. This led to his admission and to an operation which disclosed a cystic glioma centring at the left supramarginal gyrus. An incomplete extirpation was made and subsequent Roentgenotherapeutic sessions were instituted. He made an extremely satisfactory recovery, remains practically free from symptoms except for some hesitancy in speech, and has been actively engaged in his practice now nearly three years since the operation, though signs of a recurrence may at any time be expected. If the story of his first attack of aphasia can be relied upon as a premonitory symptom, seven years elapsed before pressure symptoms supervened, leading to operation; and since then he has done well, for three years, though a worse tumor could hardly be found in a more damaging place.

Thus these six examples of spongioblastoma multiforme which have shown the longest survival period all prove to be ones with a premonitory history of Jacksonion seizures for many years before pressure symptoms supervened. This may indicate that even these most malignant growths may have a far longer life than is commonly supposed possible, for the same tumors happening to arise in a silent part of the brain would have given no warning of their presence till the onset of pressure headaches. All of these lesions, so far as our records permit us to judge, show an increasing degree of malignancy, the recurrent tumors giving evidence of more active cell division than the original lesion. Whether deep Roentgenization ever does more than to hold the growth temporarily in check is problematical. In the last case mentioned, radiation has probably been given a more thorough trial than any case in the series.

2. THE MEDULLOBLASTOMAS.—These are rapidly growing, soft, malignant tumors which not infrequently, when they reach the leptomeninges, disseminate themselves through the sub-

arachnoid spaces. They occur with the greatest frequency in the midline of the cerebellum in childhood (Fig. 88), though tumors of similar histological structure have in four cases been identified in the cerebrum. They are probably no less malignant than the spongioblastomas just described, their more favorable position in the table on page 108 being due to the influence of four cases referred to below.

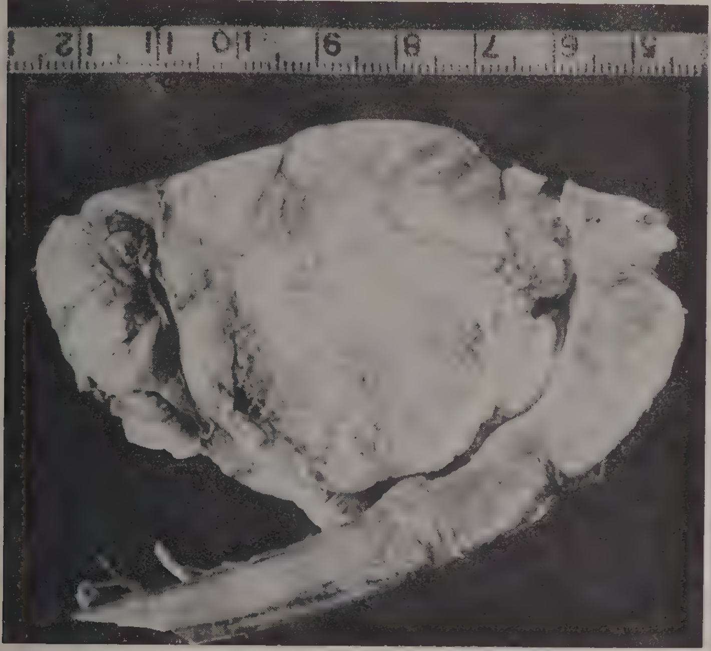

FIG. 88.—Mesial section of large midcerebellar medulloblastoma (P.B.B.H. Surg. No. 320). A child of six entered Aug. 1913, after five months' headaches, vomiting and instability. Recent opisthotonoid seizures. Emergency suboccipital decompression with ventricular puncture. Early fatality from respiratory failure. (Natural size.)

The average age of the 25 cerebellar cases in the series * was 10 years—the youngest being 2, the oldest 38 years. As a

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* These 25 cerebellar medulloblastomas in children were first reported in June, 1924 (*cf.* footnote, p. 113), as spongioblastomas, but to avoid confusion with the tumors described by Globus and Strauss,[24] the name has been changed.[3]

matter of fact, 16 of the cerebellar cases occurred in the first decade of life. The 4 cerebral cases, on the other hand, were in older patients with an average age of 36 years.

Attention has already been called to the common point of origin of these tumors over the roof of the fourth ventricle, and until recent years they have been considered beyond the possibility of surgical removal. In the earlier cases in the series, consequently, little more was done than to expose the lesion, and possibly to remove a fragment for histological verification.

The clinical story, after symptoms have once manifested themselves, may be very brief, if one is to judge from the survival period of three months for the two cases which died before an operation could be carried out. The averages for the series as a whole show approximately six months before operation and six months after operation—a year in all. However, we have latterly had one or two apparently successful extirpations, for the growth, after all, in its early stages and before it comes to " infect " the meninges, does not actively invade the cerebellar tissues, so that under favorable circumstances, in spite of its desperate situation, a more radical attempt at extirpation than has commonly been made in the past may be justifiable.

Radiation, moreover, appears to have considerable effect in deterring the growth of the undifferentiated cells of which these lesions are composed, as one might expect from the law of Bergonié and Tribondeau. We now have one patient (Surg. No. 13981) living four years after a primary operation followed by deep Roentgenization, and who six months ago had what appears to be a total enucleation of the growth, which was only fragmentarily removed at the first session. Consequently, although these tumors may be considered to be among the more malignant of the gliomas, and though recurrence is likely

(Fig. 89), they are by no means hopeless surgical problems now that we know something definite of their character and customary anatomical situation. Four of the somewhat more radically treated cases in the later series, the last three of them thoroughly radiated, have survived for 41, 51, 65, and 72 months, respectively.

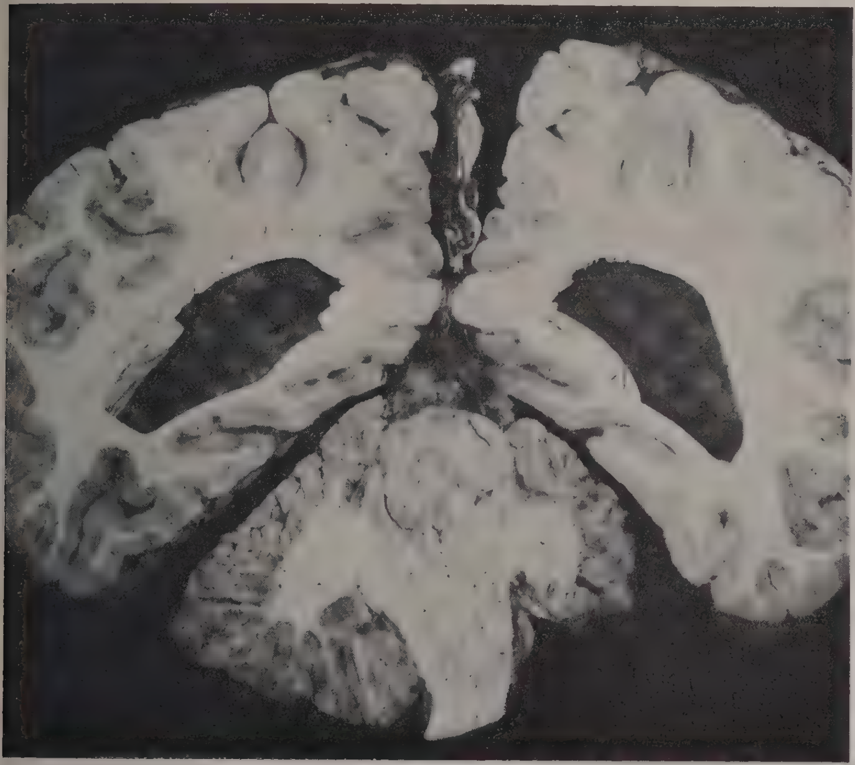

Fig. 89.—Recurrence of a medulloblastoma (Surg. No. 19775) overlying fourth ventricle and blocking the iter, with fatality three months after extensive operative removal. (Four-fifths natural size.)

When these tumors occur, as they most commonly do, in the midline of the cerebellum, the prognosis is affected by the inevitable early hydrocephalus as much as by the serious nature of the lesion itself, for a suboccipital decompression may give marked temporary relief, even though the lesion is left to pursue its course. Thus in a recent case (*cf.* Fig. 90) the patient remained practically free from symptoms for 12 months after a decompression, with subsequent X-ray treatment, when a sudden fatality occurred from a spontaneous hemorrhage into the tumor—a most unusual occurrence.

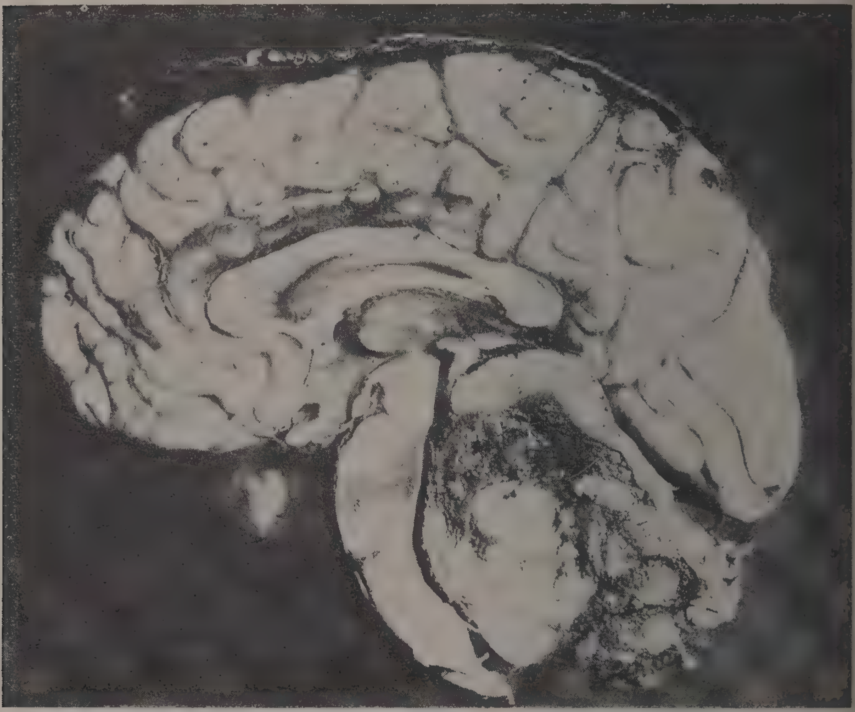

Fig. 90.—Midsection of brain (Surg. No. 24233) to show position of cerebellar medulloblastoma. A child of ten who had had a year's complete freedom of symptoms after a cerebellar decompression performed elsewhere with subsequent radiation. Sudden death from hemorrhage into tumor occurred before secondary operation could be performed. Note the sharp demarcation of the tumor from cerebellum and brain stem. (Three-fifths natural size.)

5. The Pinealomas.—There have been five examples with an average survival period of 18 months. From the place

given to these tumors on Schema IV, one would expect them to be more slow-growing than they appear to be, and to have a longer life; but as a matter of fact, the neoplastic cells of which they are composed are not fully developed parenchymal cells, so that on histogenetic grounds they should possibly be placed somewhere higher in our schemic representation. Be this as it may, they are probably less malignant tumors than the pineoblastomas, and probably would show a longer survival period were this not affected by secondary considerations which concern pineal tumors of any sort: namely, the inevitable and early obstructive hydrocephalus.

Unlike the pineoblastomas, the five pinealomas, with one exception, were not operated upon, and this may possibly be an element affecting their longer survival period, but the cases are too bizarre in other respects to place reliance on this explanation alone. The longest-lived case, curiously enough, was one of the two examples of double tumor—a glioma of the chiasm accompanying a large pinealoma.* The patient had been having severe headaches for three years, and a bilateral subtemporal decompression had been performed before his admission. When he first came under our observation, there was marked emaciation, paralysis of conjugate upward movement of the eyes, a choked disc, and polyuria. The condition was evidently inoperable, and death ensued seven weeks after his admission.

The other instance of double tumors, mentioned when considering the medullo-epitheliomas, is also included, the small pineal tumor having of itself no possible influence on the fatality. Another of the patients died from tuberculosis; still another after a ventricular puncture. It is therefore impossible to draw any dependable conclusions from such variable data.

Like the pineoblastomas, these tumors also were lesions of young adult life, the average age of the patients being 17 years on admission, two years older than for the pineoblastomas. Only one case showed *pubertos precox,* a condition known to be more commonly associated with teratomas of the pineal. A clinical study of these pineal lesions as a whole shows that the primary symptom is almost invarably a general headache, due to ventricular distention, though characteristic oculomotor signs are almost certain to appear in course of time. Pineal tumors in

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* Horrax and Bailey, Tumors of the Pineal Body, *loc. cit.*, Case VIII.

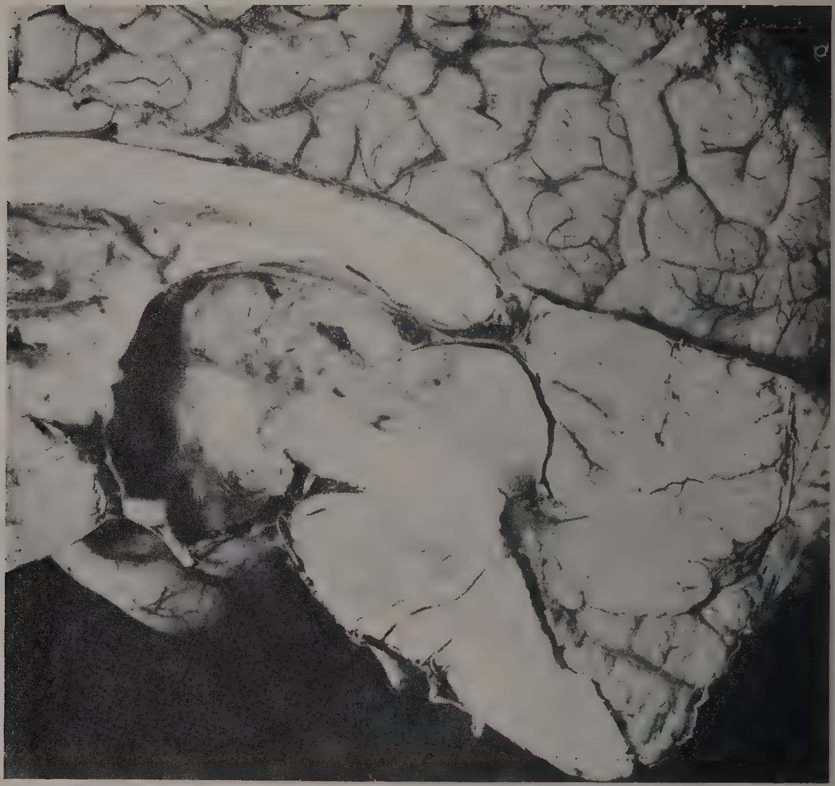

Fig. 91.—Gross appearance (natural size) of a pinealoma (Surg. No. 21567) which had caused general pressure symptoms of twelve months' duration. Death followed ventriculography. (*Cf.* Fig. 54.)

this respect differ from pontine tumors, in which oculomotor symptoms almost invariably precede the headaches. We are likely to make more exact localizing diagnoses in the future, but it is improbable that we shall ever be able successfully to extirpate these lesions in view of their inaccessible position; and our knowledge of them is likely to be gained almost solely from autopsy specimens. From all points of view, they are most unfavorable lesions. A typical example is shown in Figure 91.

6. The Ependymoblastomas.—This is another small group which, like the preceding, comprises only five identified examples, a number too small for any definite conclusions regarding prognosis. As a matter of fact, the position of these tumors, given in Schema IV, is perhaps misleading, for they are possibly no more malignant than the ependymomas, both groups representing lesions which are particularly serious because of their customary seat of origin. In all certainty they lie dormant for many years before giving any indication whatsoever of their presence.

In an earlier paper by one of us (Bailey [2]) on the subject of ependymal tumors in general, no attempt was made to distinguish the ependymoblastomas from the somewhat more highly differentiated ependymomas. The majority of the tumors of both sorts occur in the midcerebellar region in much the same situation as the medulloblastomas heretofore considered. But with experience they can be distinguished from one another at operation by their gross characteristics. The soft reddish medulloblastoma differs markedly from the more firm, pale, and sometimes nodular ependymal tumor, which has a still greater propensity than the medulloblastoma to project downward within the posterior cistern into the spinal canal. It is because of this propensity that the mere operative exposure of these lesions, regardless of any attempt at extirpation, is an operation of magnitude. The first symptoms, which often come on abruptly, are presumably due to obstructive hydrocephalus, and from this onset few months are likely to elapse before the patient seeks surgical relief. A localizing diagnosis is usually not difficult, owing to suboccipital discomforts with some evidences of cerebellar involvement.

The operation in the five cases has consisted of the usual wide bilateral suboccipital exposure, and the tumor has almost always been apparent between the cerebellar tonsils over the region of the fourth ventricle, differing in this respect from the medulloblastomas, which usually are exposed only after a median vertical incision through the posterior portion (uvula) of the vermis. In four of the cases it was necessary for a satisfactory exposure to remove the posterior arch of the atlas and to carry the incision down to the axis, and in one case to remove the posterior arch of the axis as well, and to incise the spinal dura down to the third cervical laminæ before the lower end of the intraspinal portion of the tumor could be brought into view. At operation little more has customarily been done than to remove this intraspinal projection of the tumor for purposes of identification and to liberate the medulla from pressure.

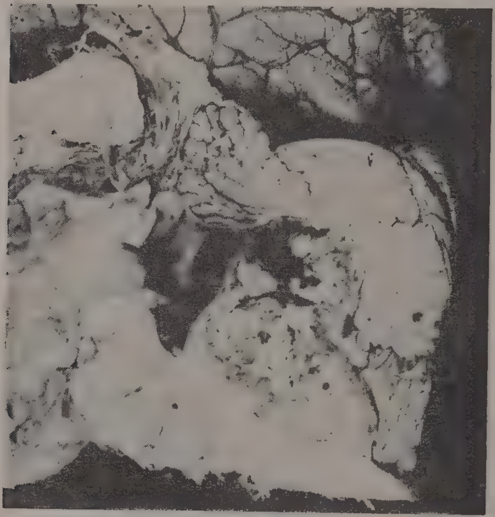

Fig. 92.—To show on midsection of cerebellum an ependymoblastoma, arising from the floor of the fourth ventricle, which has produced marked internal hydrocephalus. The tumor can be seen extending backward into the spinal canal, together with the foraminal cone of the cerebellum. It shows a markedly degenerated core with an area of hemorrhage. Kindness of Dr. William Boyd.

Having had no opportunity for a post-mortem examination in one of these cases in which the lesion had been left intact, we give here (Fig. 92) a photograph of such a tumor which has been sent to us for identification by Dr. William Boyd, of Winnipeg. The chief facts regarding the five ependymoblastomas may be deduced from the following summary:

TABLE OF VERIFIED EPENDYMOBLASTOMAS.

No.	Age	Duration symptoms before operation	Situation	Operation	Survival
2389	11 yrs.	5 mos.	IVth Vent.	I. Decompression + atlas + axis; fragmentary removal II. Attempted extirpation 13 mos. later	13 mos. Fatality
5901	4 yrs.	4 mos.	IVth Vent.	Decompression; fragmentary removal	21 mos.
13276	34 yrs.	18 mos.	IVth Vent.	Decompression + atlas; fragmentary removal; X-ray	6 mos.
17363	7 yrs.	3 mos.	IVth Vent.	Decompression + atlas	Fatality Hyperthermia
18049	10 yrs.	6 mos.	IVth Vent.	Decompression + atlas; X-ray	Living and well 29 mos.

The average age, therefore, has been 13 years, the average duration of symptoms 7 months, and the average survival period after operation 11+ months, or, if the two operative fatalities are excluded, 19+ months.

As already stated, the tumor is certainly much less malignant than these figures would indicate, and as it is inevitably found fully developed, it is almost certain that the neoplasm has been under way possibly for a matter of some years rather than of months, as the histories would indicate.

Since January 1, 1924, a typical ependymoblastoma (not included in this series) has been successfully removed from the cerebrum, a large enucleable tumor apparently removed in its totality, and the patient is now, a year later, perfectly free from symptoms. It is probable that all the fourth ventricle tumors of similar nature might be correspondingly treated were it not for their dangerous situation; indeed, they may come to be more vigorously attacked in the future now that we know something more of their histologically favorable character.

7. THE NEUROBLASTOMAS.—As heretofore mentioned, the diagnosis of neuroblastoma in years gone by had not infrequently been given to the tumors in this particular glioma series which we have described as medulloblastomas. Indeed it was for long the only term used to distinguish any special type of glioma from the group as a whole. We, however, have come to believe that the term is a misnomer for the medulloblastomas, though their histological architecture may often show formations resembling rosettes which characterize the sympathicoblastomas. But this alone is not a sufficient justification for the designation of neuroblastoma.

A true neuroblastoma is one in which the cells are potentially dividing toward the neural rather than the glial elements of the brain, and as such they are exceedingly rare tumors, only three examples having been identified in the series. In gross appearance they are sharply demarcated and relatively benign lesions, and were it not for the fact that two of the patients died after unsuccessful efforts to extirpate the huge growths which were found, the group might well enough have found a place much lower in the table on page 108. Earlier diagnoses and more prompt operations might easily have resulted in permanent cures for each of these cases and have left the neuroblastomas as possibly the most favorable lesion from a survival standpoint in the entire series.

All slow-growing brain tumors such as these are apt to become calcareous, and thereby to have their presence and situation made recognizable by X-ray shadows.* The three neuroblastomas share in this characteristic, though the first of them was observed before cranial Roentgenology was sufficiently developed to show clearly such shadows. This early case had a particularly remarkable history which deserves a brief recital if for no other reason than to show how loath doctors were to make a diagnosis of cerebral tumor a short two decades ago.

A child of 10, the daughter of a naval officer, was admitted to the Johns Hopkins in May, 1907 (Surg. No. 20638), with the story that in the summer of 1904, while playing one day in the Luxembourg Gardens and perfectly well, she had a sudden uncontrollable jerking of her left arm. Similar attacks soon followed. They were regarded by the Parisian neurologists and children's specialists called in consultation as hysterical, and she was six months under a psychotherapeutic régime. But as the attacks continued and her left side became affected, it was presumed that some cerebral infection (encephalitis?) was the underlying cause.

Matters went from bad to worse during the ensuing three years; her left side became spastic, and orthopedic exercises were instituted. Finally her head began to enlarge, the left hemiparesis increased, and a neurologist in Naples made a diagnosis of hydrocephalus, put the child on iodides, and had his surgical colleague puncture the ventricle. This was done eight times, a small amount of xanthochromic fluid being removed on each occasion, with temporary improvement. The child meanwhile had become practically decerebrate. She was taken to a surgeon in London, who, accepting the diagnosis made in Naples, namely, of luetic meningitis with hydrocephalus, undertook to establish a permanent bilateral drainage for the cerebrospinal fluid by the insertion of gold tubes which led from the subarachnoid space to the subgalea aponeurotica. At this juncture the child's father was ordered to Annapolis, and the patient was referred to the Johns Hopkins Hospital.

On admission the child was in a state of what would today be recognized as extreme decerebrate rigidity. There was a large hydrocephalic head which bulged especially on the right side, where was a pressure defect in the skull. She was in a continued profound stupor, from which she might occasionally be aroused to speak in a few monosyllables. She swallowed liquids well and her nutritional condition was fair. The eye-grounds showed an apparent atrophy without choked disc.

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* A special study of this matter has been made by Dr. Arthur van Dessel[16] of the cases in the series. It appears that since the introduction of the Potter-Bucky diaphragm in the hospital early in 1921, about 13 per cent. of the verified gliomas have shown shadows of calcareous depositions on the X-ray films. All of them proved to be tumors of slow-growing type.

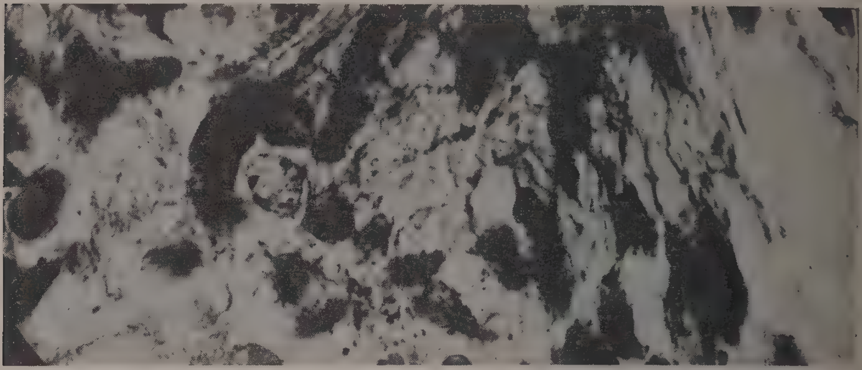

Fig. 93.—(Surg. No. 20638.) Photomicrograph (× 850) of section stained with phosphotungstic acid-hematoxylin on which the diagnosis of glioma was made in 1907. The fibrils which appear black in the photograph are red in the section. Only the nuclei of the cells are stained.

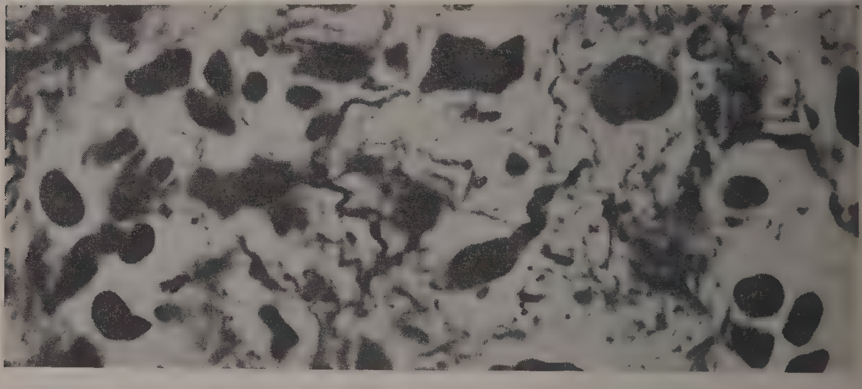

Fig. 94.—For comparison with Fig. 93. Photomicrograph (× 850) of section prepared with Cajal's pyridine silver method which specifically impregnates both cytoplasm and processes, making it certain that the cells are unipolar neuroblasts and the tumor therefore a neuroblastoma.

Under the belief that the early attacks must have been Jacksonian in character and been due to a right-sided tumor, an osteoplastic exploration was made, and a huge, evidently enuncleable growth was exposed. A few days later an attempt was made to remove the massive growth, which nearly filled the hemisphere. There was an early fatality.

The tumor, which weighed nearly 400 grams, was highly calcareous, and at the time a pathological diagnosis of angiolithic glio-sarcoma was made. Sections showed what was then properly called a glioma, and Figure 93 shows a photomicrograph of the preparation made at the time. This may be contrasted with the tumor in approximately the same magnification as now stained by Cajal's reduced-silver method. (Fig. 94).

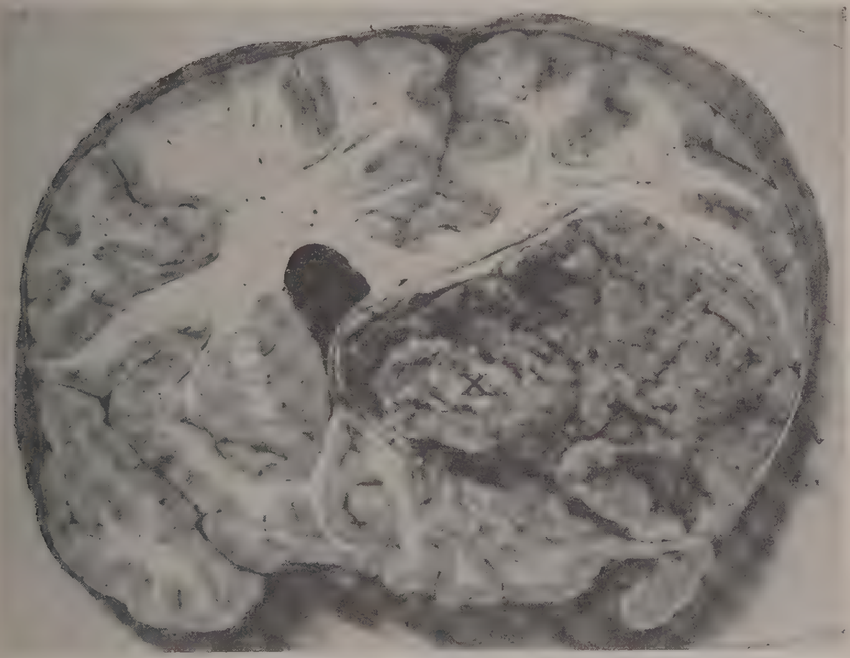

Fig. 95.—Showing a large neuroblastoma from the case (Surg. No. 15265) described in the text. The calcareous nodule, measuring about 2 cm. in diameter, centres at the point marked with an X. (Four-fifths natural size.)

The second case was that of a farmer, aged 30, who was admitted to the Brigham Hospital (Surg. No. 15265), September 27, 1921, with the story of having been perfectly well until ten days before, when he consulted his local doctor because of a frontal headache. A lumbar puncture gave temporary relief, but the discomforts soon returned with nausea and vomiting, and he was sent to the hospital. A detailed examination showed a bilateral choked disc of 6 D., and some questionable weakness of the right side, bilateral hyperactive reflexes, and a dorsal toe response on the left. He at times was slightly disoriented. An X-ray was taken which disclosed a calcareous nodule the size of a robin's egg near the midline low in the left frontal lobe.

Three days after admission he had a sudden unlooked-for exitus from respiratory failure. The autopsy disclosed an unexpectedly large tumor, which must have been present for many years and have slowly distorted the brain without giving antecedent local symptoms (Fig. 95). The tumor, which shows typical rosettes, was called at the time a neurocytoma (*cf.* Figs. 24, b and 79), in this instance a correct diagnosis.

The third case was a man of 41 (Surg. No. 16313) who was admitted in March, 1922, as a case of pituitary tumor. He had been perfectly well until four months previously, when he began to have headaches and blurred vision. Examination showed a bilateral choked disc advancing to atrophy, but the neurological findings were practically negative. There was a tender spot on the skull over the right fronto-parietal region, and on auscultation a systolic bruit was heard over the cranium. The X-ray showed local thinning of the skull in this region with a subjacent shadow, which led to a diagnosis of meningioma. An osteoplastic exploration exposed the margin of a glioma. At a second sitting a mass of what proved to be a well-demarcated tumor the size of a fist was extirpated. It was soft, unusually vascular, and was incompletely removed.

He made an excellent post-operative recovery, and, aside from the disability due to deterioration of vision, remained vigorous and well for two years and four months, when for some unexplained reason he suddenly became comatose and died.

The tumor was diagnosed "glioma," but our review of the tissue shows definite neuroblasts (*cf.* Fig. 81, b). Had we known enough about these lesions at the time this man would certainly have been recalled for a secondary operation.

Attention may be drawn to the fact that all these three tumors attained an enormous size, that all three of them showed calcareous depositions, and it may be assumed that all three were of long standing, and that the tumor certainly long antedated the onset of the final pressure symptoms. One can hardly arrive at any dependable conclusion as to the average longevity of neuroblastomata from a small series, in which one patient after the onset of local symptoms lived three years before a fatal operation, in which another died within two weeks after the first symptoms, and in which a third lived over two years after a partial extirpation. Nevertheless the figures suffice to show even without calling on the microscope, that these lesions are not to be confused with the short-lived tumors which we choose to term medulloblastomas.

From the preceding remarks it may be gathered that the neuroblastomas are to be regarded as more favorable tumors than their position in the table on page 108 would indicate. However this may be, from now on we are to deal successively with varieties of gliomata, which on the basis of actual statistics rather than of clinical impressions, tell, so far as longevity is concerned, a far more encouraging story. We come for the first time to a list of cases which show a progressively increasing number of survivals beyond the eighteen months which have elapsed since January, 1924. There are now living of the:—

Astroblastomas	1 out of 13 or 7.7%
Ependymomas	1 out of 7 or 14.3%
Unipolar spongioblastomas	2 out of 9 or 22.2%
Oligodendrogliomas	3 out of 9 or 33.3%
Protoplasmic astrocytomas	18 out of 52 or 34.6%
Fibrillary astrocytomas	22 out of 39 or 56.4%

Thus to take the totals of these 129 cases, which represent one-half of all the classified tumors, 47 cases, approximately one-third of them, are still living over periods varying from 18 months to 20 years. We may now consider these more favorable and somewhat more highly differentiated forms of glioma.

8. The Astroblastomas.—We have seen that the astroblasts develop from the unipolar spongioblasts and are characterized by having a single long process which is attached to the wall of a blood-vessel. The tumors, largely composed of these cells, of which there are thirteen examples in the series, unlike those of the preceding group, are infiltrating, and show no tendency toward encapsulation (Fig. 96). They nevertheless are slow-growing, rarely showing mitoses, though amitotic division is common. They have a survival period averaging 28 months for the group as a whole, though one of the cases had

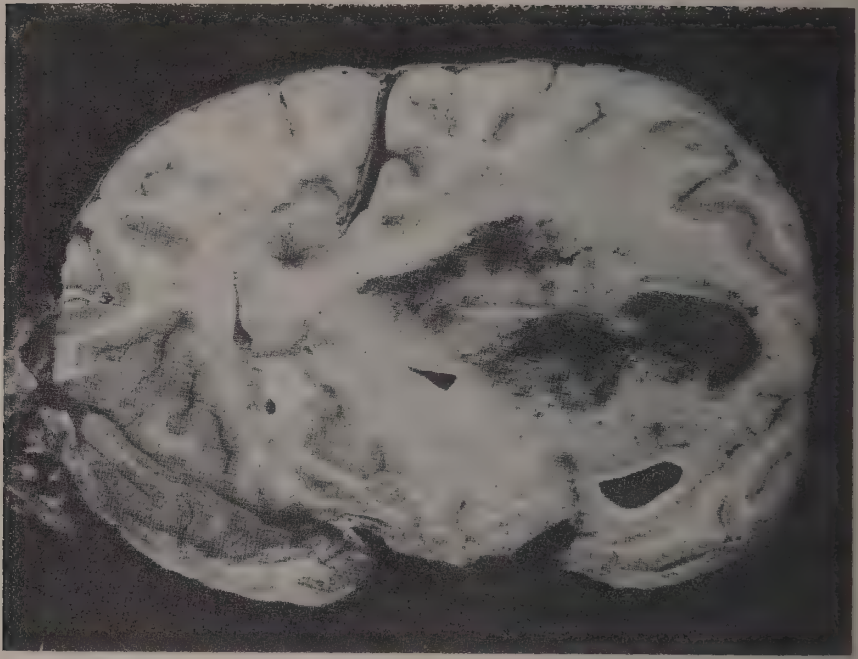

Fig. 96.—A large left frontal astroblastoma (Surg. No. 15081) extending backward through the major part of the hemisphere. The patient, aged twenty-seven, after four years of headaches with disturbance of vision was admitted in coma May 1921. The lesion was not localized and a right subtemporal decompression was performed. Readmission three months later when a fatality occurred after a misdirected exploration. Note the presence of a small cyst, the evidence of recent extravasations and total absence of any peripheral demarcation of the lesion even though relatively benign. (Two-thirds natural size.)

a history lasting over fifteen years, which perhaps unduly affects the general average of so small a number of examples. The 13 tumors have all occurred in the cerebral hemispheres, and have been invariably subcortical. They are tumors of adult life, chiefly of the fifth decade, the average age of the patients being 42 years. A few examples of the longer-lived cases in the series may be referred to.

One patient in the Johns Hopkins series (No. 21984) lived from the onset of symptoms for five years and seven months. This was a man of 36, who for three and a half years had had typical uncinate seizures with a left hemianopsia. At operation there was disclosed a large temporal lobe cyst with tumor at its base. The cyst became replaced by solid tumor, and he died some months after a secondary operation with partial extirpation of the growth.

Another case in the Brigham series (No. 1114) lived 5 years, after a negative exploration for focal epilepsy performed elsewhere. Pressure symptoms finally supervened, and an attempted extirpation of a large tumor led to a fatality. Still another (No. 16909) had had periodic severe headaches with vomiting for fifteen years, with a sudden exacerbation six weeks before admission, when a negative exploration was performed which led to a fatality from bleeding into the tumor.

Though these were long-lived cases from the standpoint of duration of symptoms, little of prognostic value can be gained from them, because of their post-operative misfortunes. The single case in the series of 13 which offers encouragement is the one patient still living who has been thoroughly radiated since her tumor extirpation. A brief statement of the case follows:

Surg. No. 19514. Mrs. S., aged 43. For two months she had been having frontal headaches with convulsive attacks and numbness involving the right arm. Examination showed right hemihypæsthesia, with exaggerated reflexes and complete astereognosis in the absence of a choked disc. At operation on August 23, 1922, a tumor was disclosed on incising the cortex of the parietal lobe, and a solid lesion about the size of a hen's egg, considered to be a glioma, was enucleated. It proved to be composed of astroblasts having little cytoplasm, a few astrocytes, and no differentiated neuroglia-fibrillæ. The operation produced a marked hemiplegia with aphasia, from which she has largely recovered, to the extent that she earns her living as a photographer, and at this writing, three years later, remains well and free from any evidence of recurrence. She has had a succession of deep X-ray treatments, which may have been influential in holding the lesion in check.

9. The Ependymomas.—What has been said in regard to the ependymoblastomas largely applies as well to these more highly differentiated tumors of the same histogenesis. Though blepharoplasten still persist in the ependymomas, the cells have become polygonal, and their tails have for the most part disappeared. They might be expected to be more slowly growing lesions, and their position in Table IV points in this direction. But in their case also, the fact that they often arise from the walls of the fourth ventricle or, as in one instance, from the septum lucidum (Fig. 97), is a modifying element, for these are bad places for even a benign lesion.

It is probable that the life of these tumors is far longer than indicated by the recorded first onset of symptoms. These are usually headaches, with nausea and vomiting a pronounced feature; and a suboccipital decompression may serve to relieve all symptoms for months or years. There is one remarkable case among our unverified tumors, necessarily excluded from our present list, though it is almost certainly an ependymoma. The case is mentioned in Bailey's first paper,[2] the tumor having been exposed at operation, when a sketch was made of it without taking tissue for verification. The patient was then a woman of 25; she was operated upon thirteen years ago, and has since remained perfectly well and become the mother of four healthy children.

For comparison with the list of ependymoblastomas, the seven ependymomas may be similarly tabulated. Only the first four of them, as will be seen, were fourth-ventricle tumors.

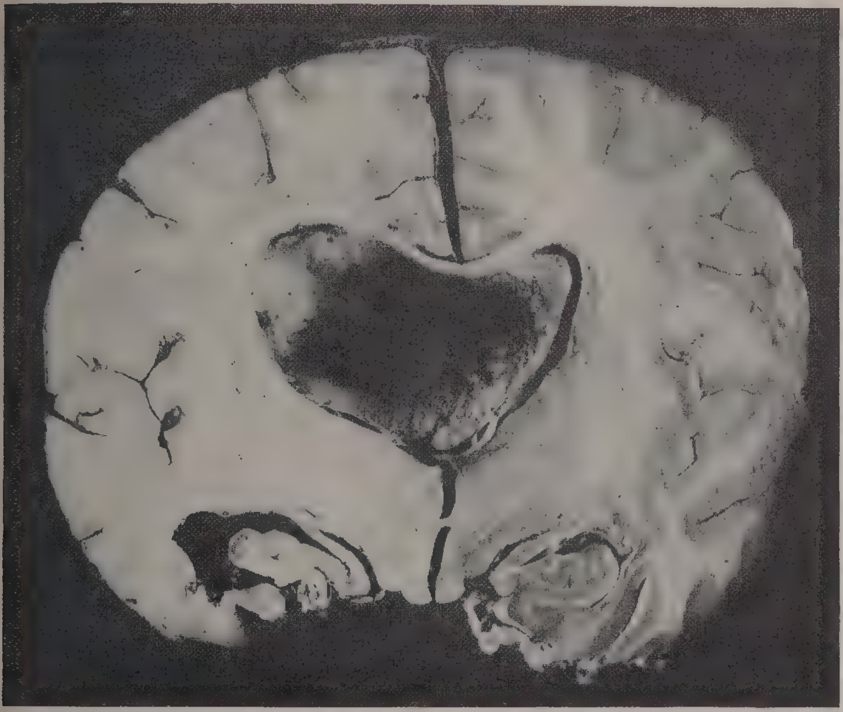

Fig. 97.—An ependymoma arising from the septum lucidum in a patient aged twenty four who had had two years of headaches before tumor was suspected. An attempted ventricular puncture for purposes of ventriculography caused a fatality from hemorrhage. (Four-fifths natural size.)

The average age, therefore, is 23 years, ten years older than for the ependymoblastomas, though this may be fortuitous. The average duration of symptoms, often regarded as gastric in origin, preceding admission was 18 months. The average survival period after operation was 16+ months, or if the two

TABLE OF VERIFIED EPENDYMOMAS.

Surg. No.	Age	Site	Admission	Symptoms of Onset	Operation	Survival	Total
357	36	Cerebellar recess	Aug. 29, 1913	48 months; headaches and vomiting	(1) Subocc. decomp., Sept. 3, 1913 (2) Evac. cyst, Feb. 13, 1914 (3) Attempted enucleation with fatality, July 16, 1914	10 mos.	4 yrs., 10 mos.
1227	23	IV ventricle	May 15, 1914	2 months; vomiting and headache	(1) Subtemp. decomp., Sept. 1912 (2) Ventric. punct.; fatality, May 15, 1914	20 mos.	1 yr., 10 mos.
3772	41	IV ventricle	Oct. 27, 1915	14 months; vomiting	Suboccip. and altas, Oct. 29, 1915	24 mos.	3 yrs., 2 mos.
4764	11	IV ventricle	May 21, 1916	8 months; headache and vomiting	Transcortical extirp., May 25, 1916	Fatality	0 yrs., 8 mos.
13429	24	Septum lucidum	Oct. 28, 1920	25 months; headaches	Exploration; ventric. punct. c̄ hemorrhage, Nov. 1, 1920	Fatality	2 yrs., 1 mo.
15442	22	Supramarginal gyrus	Oct. 24, 1921	10 months; headaches	(1) Evac. of cyst + tumor, Nov. 1, 1921 (2) Evac. of cyst + tumor, Apr. 13, 1925	3 yrs., 8 mos.+	4 yrs., 6 mos.+
19422	7	Occipital lobe	Aug. 10, 1923	21 months; convulsions	(1) Explor. neg., Aug. 15, 1923 (2) Explor. evac. cyst, Oct. 6, 1923 (3) 2nd stage. enuc., Oct. 10, 1923	13 mos.	2 yrs., 10 mos.

operative fatalities are excluded, 22+ months. A brief history of the only patient in the series who survives with possibility of cure is as follows:

A frail young woman of 22 (Surg. No. 15442) was admitted in October, 1921, with the story of headache for five years, becoming worse in December, 1920, and soon followed by numbness and weakness of the right side with aphasia. She showed an advanced choked disc, an homonymous field defect, and the X-ray disclosed a deep-seated calcareous shadow.

At operation, Nov. 1, 1921, a large gliomatous cyst was opened, and at the bottom of the cavity a slightly calcareous mural tumor-mass was disclosed and partially removed. Her symptoms entirely disappeared.

She subsequently married, gave birth to a child in August, 1924, and shortly after this her paralytic symptoms reappeared without headache or other evidences of pressure.

She reëntered the hospital in April, 1925, when at a second osteoplastic operation under novocaine the cyst was found to have refilled. It was again opened and a nodule of tumor in its wall was identified and apparently enucleated *in toto*. The walls of the cyst were " fixed " with formalin. She again made a perfect surgical recovery and it is hoped may now be spared any possible further recurrence.

10. THE UNIPOLAR SPONGIOBLASTOMAS.—Nine examples have been found in various parts of the brain with a predilection (six cases) for the cerebellum. Two were thalamic (*cf.* Fig. 98) in origin and one frontal. The average age of the patients on admission was 15 years, the youngest 3, the eldest 41, so that on the whole they are tumors of early life.

Their average survival period as shown in Table IV is nearly four years. This is at variance with what one might theoretically expect from their histogenesis, but there can be no doubt of their chronicity. Some of the tumor sections show a variable number of bipolar spongioblasts, and it is possible that the cells represent a differentiation in the direction of the cells composing the neurilemmal sheaths. From this viewpoint, they may perhaps be allied to the peripheral neurinomata, it

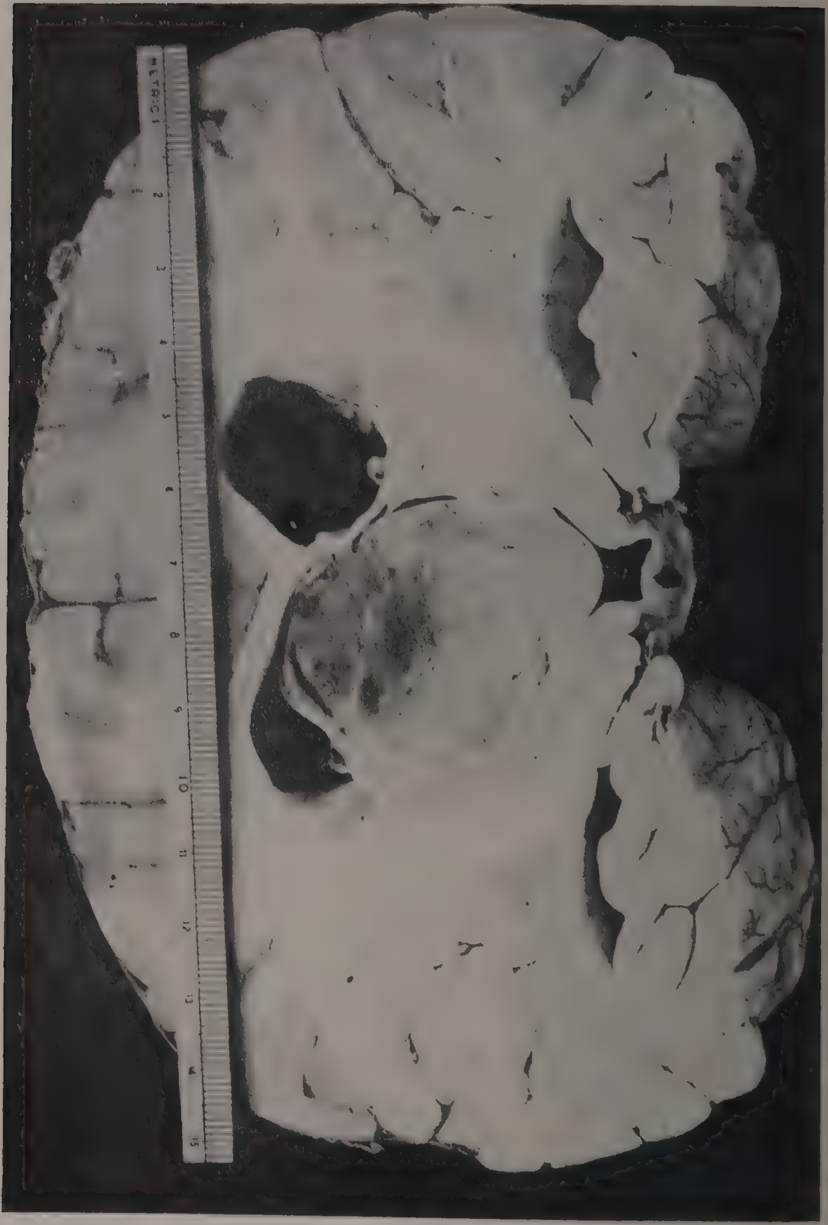

FIG. 98.—Spongioblastoma unipolare (Surg. No. 1963). A blind girl of sixteen with six months' symptoms suggesting a cerebellar tumor with hydrocephalus; suboccipital exploration with fatality from respiratory failure on the fourth day. (*Cf.* Fig. 71 a and b.)

having been shown by Kuntz, and later by Harrison, that a certain number of medulloblasts wander out on the nerve fibres to be transformed into the cells of Schwann.

A patient in the Johns Hopkins series had the longest recorded survival period—something over nine years. The story is briefly as follows:

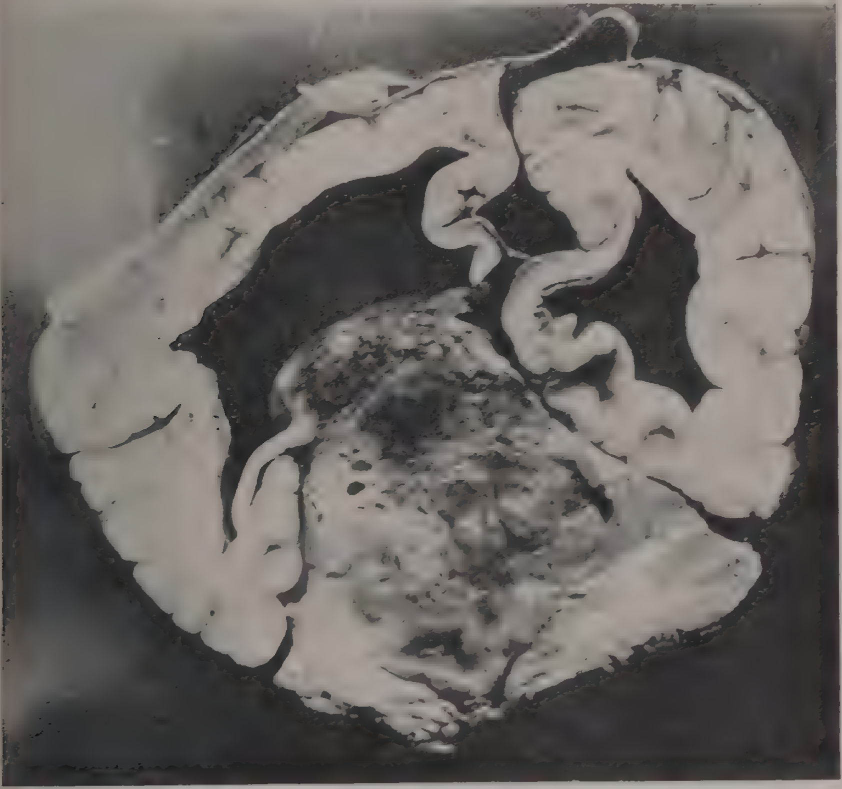

Fig. 99.—A solid unipolar spongioblastoma of the cerebellum from the case (J. H. H. Surg. No. 26647) mentioned in the text. The extensively hydrocephalic hemispheres have collapsed as the brain was not fixed before removal. (Two-thirds natural size.)

A child, aged 5, was admitted in September, 1910 (J. H. H., No. 26647), with the history of three months of vomiting, occipital discomforts, diplopia and instability. There was an obstructive hydrocephalus and a cerebellar syndrome without nystagmus. A suboccipital exploration with decompression was performed, no surface lesion being disclosed. There was marked improvement, which lasted for nearly five years before a return of symptoms. These slowly advanced, and the child died in December, 1919, having been bedridden from ataxia for the preceding three months.

An autopsy was performed and the brain was forwarded to us by Dr. Cunningham Wilson. It showed a huge, partly cystic growth extending from the posterior fossa forward into the widely dilated third ventricle (Fig. 99).

Owing to the unfavorable situation of most of these tumors, they would appear to be very unpromising lesions in spite of their relative chronicity. They, however, tend to undergo cystic degeneration, and under favorable circumstances, after evacuation of the cyst, it may be possible to remove the remaining fragment of tumor in its totality. The two cases in the series which are still living are examples of this.

A boy of 5 (Surg. No. 12153) came under observation in March, 1920, with a history of vomiting and dizziness of two months' duration. He had choked discs and inconspicuous signs suggesting a cerebellar tumor. At operation a large, partly cystic growth was found in the midcerebellar region pushing its way into the spinal canal and necessitating for its exposure a laminectomy of the atlas. After evacuation of the cyst, an apparently complete enucleation of the tumor was accomplished in the course of a five-hour operation. He made a perfect recovery, and remains well and free from symptoms now five years later.

The other surviving case (Surg. No. 17186), a young woman of 21, was equally fortunate in having a large cerebellar cyst with a circumscribed tumor nodule which was apparently removed in its entirety. The operation was performed in November, 1921, and the patient remains well and free from symptoms now three and a half years later. Such experiences show that when gliomatous tumors of this type happen to be accessible they may be removed with the expectation of at least a long period of quiescence if not of cure.

11. The Oligodendrogliomas.—These tumors, of which only nine examples have been identified, get their low place in Table IV largely owing to the single example of a patient who survived 21 years after the onset of symptoms. The tumors are

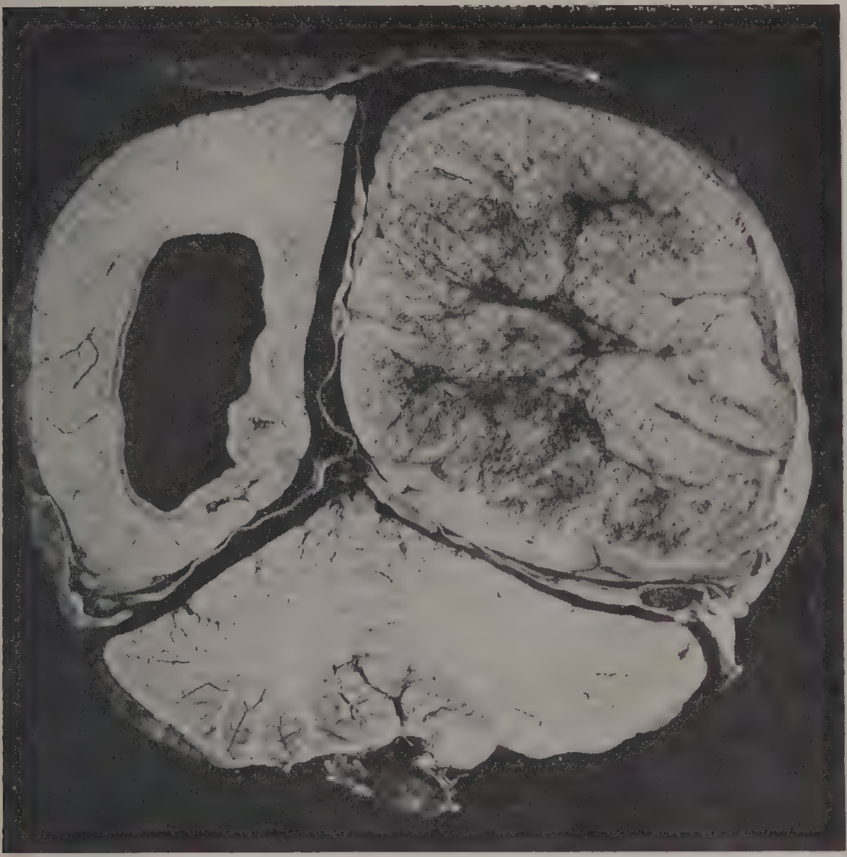

Fig. 100.—Large occipital oligodendroglioma in a child of five (J. H. H. Surg. No. 27507). Symptoms for seventeen months suggesting a right cerebellar lesion with hydrocephalus showing xanthochromia. Post-operative forty-eight-hour fatality Note the semblance in the tumor of sulci and convolutions suggesting a heterotopism. (Three-fourths natural size.)

slow-growing lesions with the appearance of encapsulation, and unless they happen to produce focal and irritative symptoms may attain a large size before they make their presence known—so large a size that their removal is well nigh impossible.

They are tumors of peculiar appearance, sometimes showing a pinkish color on fresh section, and they could hardly be mistaken for any other lesion unless possibly for a neuroblastoma. Sections of the gross autopsy specimens unaffected by operative interference may have (as in Fig. 100) the semblance of hypertrophic convolutions with deep sulci suggesting heterotopism, a characteristic, however, of some other gliomas (*cf.* Fig. 95). The absence of mitoses attests to their slow growth, as does also the tendency of the tumors to show calcareous deposits, which aid in their localization by means of the X-ray.

The youngest patient was 5 on admission and the oldest 48, the average being 29 years. But this is deceptive, for they are tumors which very possibly all start early in life. With no exceptions, the 9 cases have been found in the cerebrum, and originated as subcortical lesions, though they may reach and spread over the surface beneath the arachnoid like the cap of a mushroom. The tumors have invariably been solid ones with a fairly tough consistency, and in only one case, at a second operation, was the growth found partly cystic.

The lesion has been frontal in situation in four cases, parietal in two, occipital in one, and in two instances appears to have taken its origin in the septum lucidum (Fig. 101). All of the patients were operated upon, four of them on more than one occasion, with a single post-operative fatality after a misdirected operation in the case of the occipital lobe tumor. Three of the patients are living four years and more after operation, all of them having had long antecedent histories of focal epilepsy without pressure symptoms. The following is an example:

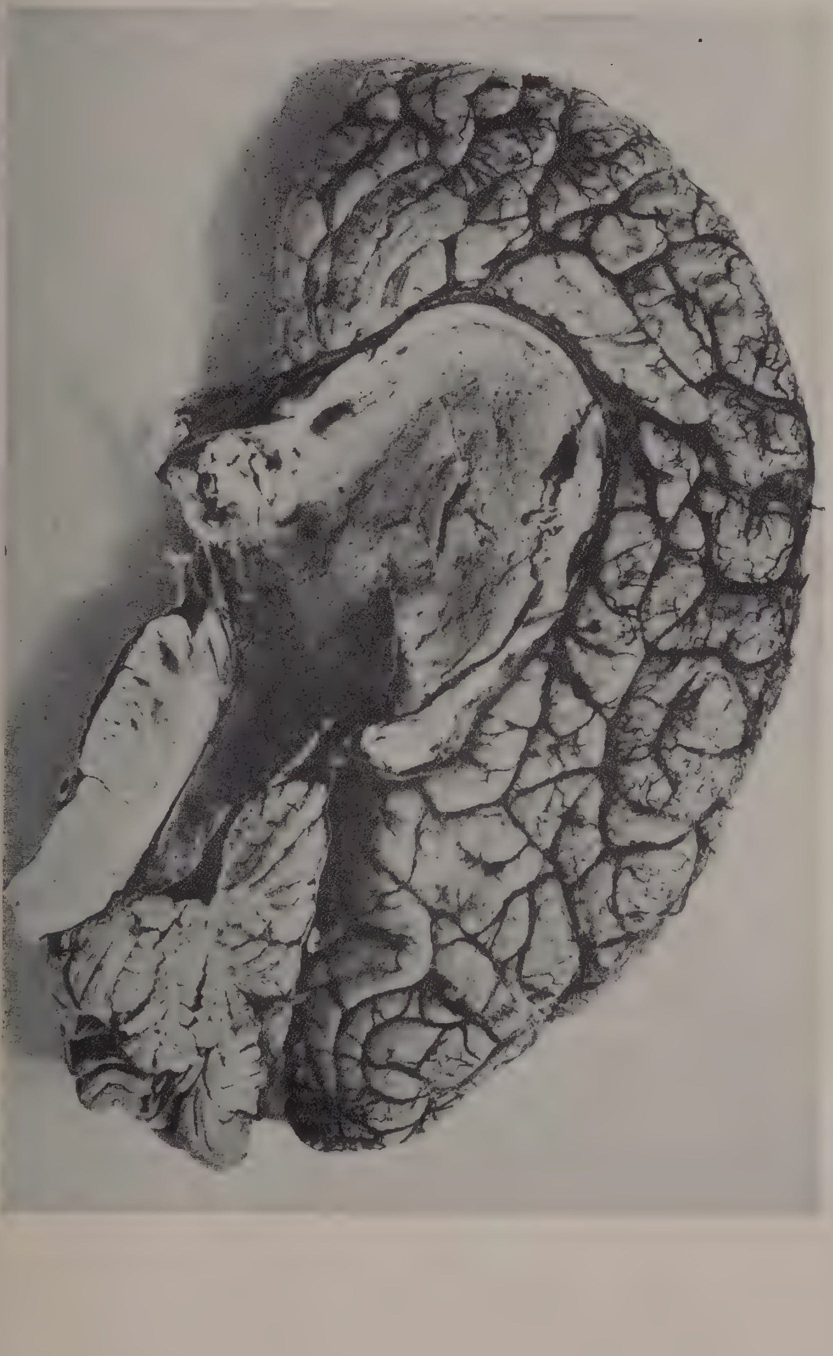

Fig. 101.—A clinically unlocalizable oligodendroglioma apparently arisen from the septum lucidum. The patient, aged seventeen (Surg. No. 12150), lived two years after subtemporal and suboccipital decompressions for the relief of pressure headaches. Note growth filling ventricles with long unattached tail projecting through the distended iter into the fourth ventricle. (Three-fifths natural size.)

A man of 43 (Surg. No. 13924) was admitted in January of 1921 after seventeen years of major and minor convulsions, which finally localized themselves as focal attacks in his right face with periods of aphasia. There had never been any pressure symptoms. The operation exposed a large firm pinkish tumor involving the left lower parietal and supramarginal gyri, and mushrooming over the adjacent convolutions. A mass extirpation was performed with only temporary impairment of the speech mechanism. A series of X-ray treatments were given. He made an excellent recovery, and except for an occasional focal attack he continued without symptoms at his occupation as a manufacturer for three years. Then a return of aphasia with, for the first time, some pressure symptoms, led to a second operation in September, 1924, when a partly cystic recurrent growth was extirpated. He again made a good recovery, and remains active and well now nine months later. The tumor was originally diagnosed as a neurocytoma.

When people of middle life begin in this way to have epileptiform attacks of obscure etiology, the possible existence of one of these slow-growing lesions must always be borne in mind. At this writing, a patient who was operated on nine years ago for focal epilepsy with negative findings has been readmitted in view of aphasia, astereognosis, and a right hemiparesis, but with no pressure symptoms whatsoever. Operation has revealed an oligodendroglioma the counterpart of that found in the case just recorded. Though the verification of this lesion has been made too late for its inclusion in the series of cases under consideration, the story is briefly mentioned to emphasize the long life of these lesions if they occupy a situation where they do not cause complications from secondary cerebrospinal fluid stasis.

12. The Protoplasmic Astrocytomas.—These represent a type which on the percentage basis proves to be slightly more favorable than the foregoing, but there are a sufficiently large number of examples to justify somewhat more definite conclusions as to their longevity. Indeed, the average survival period shown in Table IV should really be much greater than

the 67+ months there recorded, since 18 of the 52 patients of this group are still living.

Practically all of these cases have been verified at operation. Hence the opportunity to see the lesion unaltered in its relations at autopsy has been much less frequently given, and it is noteworthy in this connection that in the 81 operations on the 53 cases there were only five post-operative fatalities. Apparently, therefore, there is something about these lesions in contrast to the spongioblastomas, for example, which lessens their operative risk. It may be that there is less tendency for a cerebral œdema which, as pointed out while considering the more malignant of the gliomas, is a not infrequent and somewhat serious post-operative complication.

The average age of the patients on admission was 29 years, the cases being quite evenly distributed over the first six decades. But as many of them had shown definite local or moderate pressure symptoms from one to ten years before their hospital admission, the age of symptomatic onset of the malady would be much lower. The youngest case on admission was 23 months old, the eldest 58 years.

Of the 52 tumors, 17 were cystic, and it is doubtless due to the inclusion of many of the astrocytomas (both protoplasmic and fibrillary) in the recent study from this clinic by Martin [43] dealing with the gliomatous cysts that he was led to give such a favorable prognosis for the gliomatous cysts in comparison with the more solid tumors. His report, be it said, was made before we had undertaken histologically to differentiate the gliomas.

These protoplasmic astrocytomas are, for the most part, tumors of the hemispheres, cerebral or cerebellar, and a tabulation of the cases to determine the location of the lesion brings out the surprising fact that the 15 cerebellar cases were, with but one exception, all in young people of an average age of 13 years. In the cerebrum, there were 11 temporal, 10 frontal, and 8 paracentral lesions, with the rest scattering, the average age of these 37 patients on admission being 35 years. This may possibly be interpreted as an indication of greater longevity on the part of these tumors than we had thought possible, for it suggests that the cerebral tumors may have existed since childhood, and that the cerebellar ones merely gave earlier evidence of their presence because of their situation.

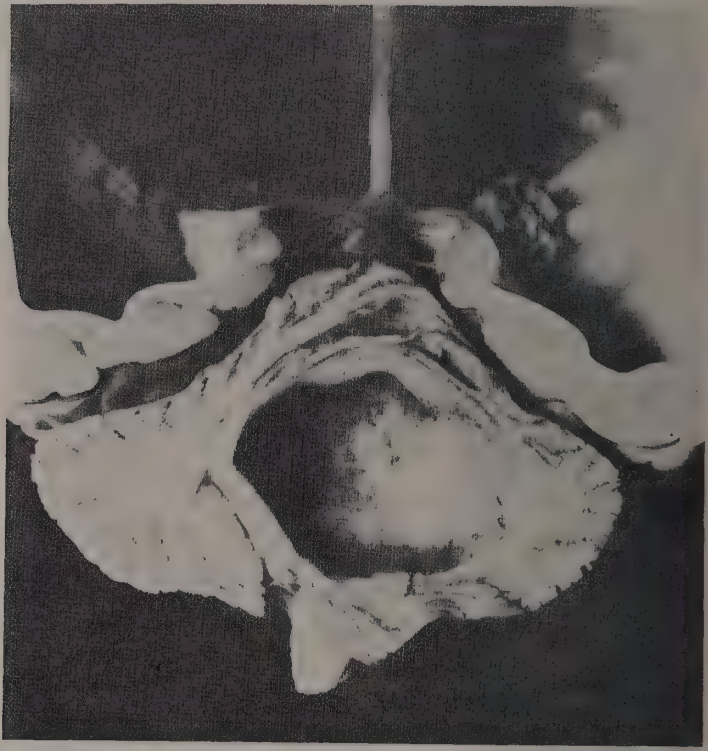

FIG. 102.—Showing (J. H. H. No. 22013) a large cerebellar cyst with a layer of protoplasmic astrocytoma in its upper wall. Secondary hydrocephalus of high degree. (Four-fifths natural size.)

The history of the youngest case in the series may be given as an example not only of one of the few operative fatalities, but as an example of one of the cystic cerebellar lesions occurring in infancy.

A physician's child, 23 months old, supposed to have an essential hydrocephalus, was admitted to the Johns Hopkins in February, 1902 (Surg. No. 22013.) The child had had gastrointestinal disturbances since birth, was supposed to have rachitis, and the fontanelles had never closed. After a fall three months before entrance, there was a sudden increase in the size of the head to a circumference of 53 cm., too heavy for the child to hold erect.

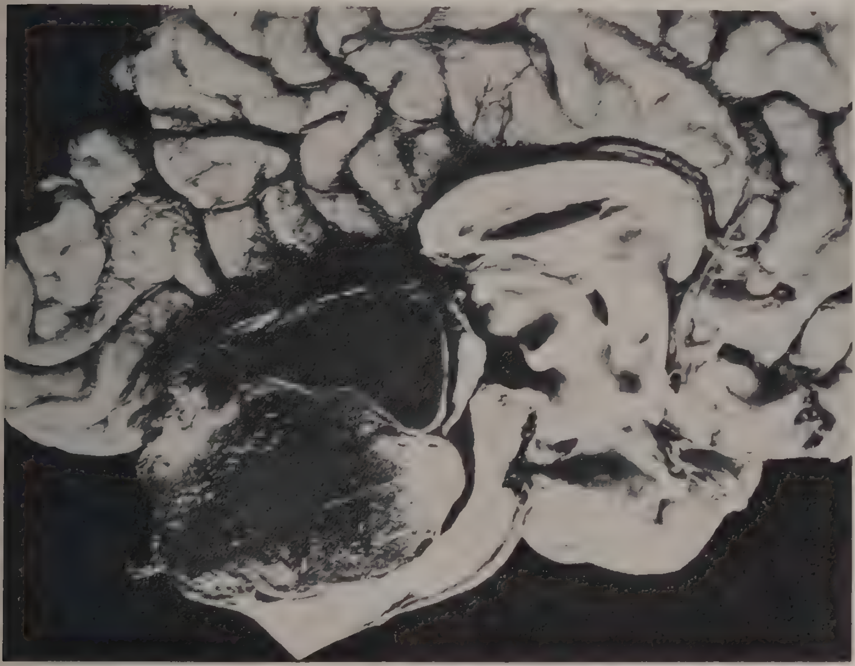

FIG. 103.—Protoplasmic astrocytoma of the cerebellum on midsection (J. H. H. Surg. No. 26829), to show the large mural tumor with overlying cyst which unfortunately was not disclosed at operation else the attempted enucleation might have been successfully carried out. (Three-fourths natural size.)

A series of combined ventricular and lumbar punctures were performed demonstrating a block supposedly at the fourth ventricle. The child improved considerably following these punctures, and operation was deferred.

She was readmitted a year later with a further advance of symptoms and a cranial circumference of 59 cm. There was marked rigidity with ataxia, and a tumor was then for the first time suspected. The operation disclosed a huge cyst chiefly in the right cerebellar hemisphere. A futile attempt was made to enucleate the cyst and its tumor cap which lay exposed at the upper part of the cyst wall (*cf.* Fig. 102). The attempt was abandoned owing to the child's condition, and death occurred three hours later.

In the 23 years which have intervened since this child's operation much has been learned about intracranial operations in general and about these suboccipital procedures in particular. Another example may be selected which shows not only technical progress but illustrates the long duration of life of some of the then unclassified gliomas.

A boy of 9 entered the Johns Hopkins (No. 26829) in October, 1910, with a history of advancing symptoms since 1906, when he was 5 years old, pointing definitely to a cerebellar lesion. He had become blind and hydrocephalic. A suboccipital exploration was performed without disclosing a tumor, but the decompression gave great relief.

On the return of symptoms he was readmitted, January, 1912, when at a second operation a large gliomateous cyst with tumor in its wall was evacuated. Again he did well for a time, but symptoms again recurred, and in January, 1914, he entered the Brigham Hospital, and an attempt was made to remove the tumor, with fatality (*cf.* Fig. 103).

In contrast to this, an example may be given of a similar lesion, also in a child, in whom the extirpation was successfully accomplished.

A boy of 14 (Surg. No. 993) after six months of headache, vomiting and failing vision, first came under observation in March, 1914. Evidences of a cerebellar tumor were unmistakable, and at operation a large cyst was found with its tumor cap presenting, so that it was possible to excise it. The walls of the cyst were then fixed with Zenker's fluid until "leathery," the cavity filled with Ringer's solution, and the wound closed. He remains well and free from symptoms now 11 years later.

Among the fifteen cerebellar cases, there are many others with a similar story, though the one just quoted, being an early example, shows the longest period of survival of any of them. The histories vary somewhat, for as in the second case cited, the lesion was not always disclosed at the first operation. This sometimes consisted in the mere evacuation by puncture of a deep "gliomatous" cyst which at a second session after a variable interval, was opened and a tumor nodule located and excised. In gliomas of this type as would appear when the mural tumor has once been found and removed, a cure may be expected.

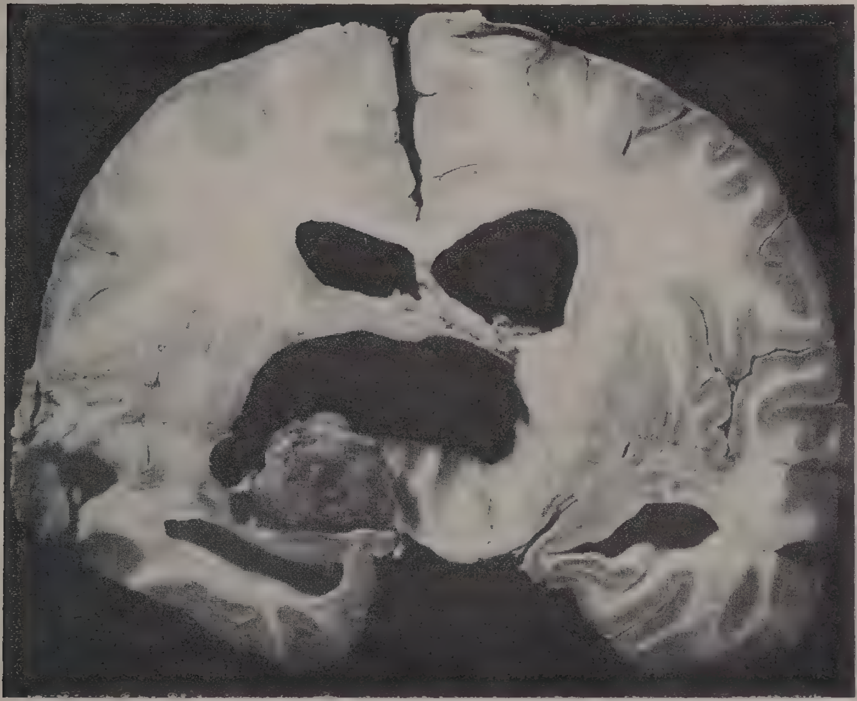

Fig. 104.—To show a cystic astrocytoma protoplasmaticum of the left temporal lobe with an enucleable mural tumor. (Surg. No. 13694.) A child of thirteen after eight months of pressure symptoms with increasing disability of the right side, was operated upon December, 1920, when a deep temporal cyst was opened and evacuated. She made a complete recovery and attended school till July, 1924, when the former symptoms began to recur. At a second operation, January, 1925, the cyst was reopened. She died suddenly three months later. (Two-thirds natural size.)

Naturally in all of these cerebellar cases in childhood there has been a relatively short premonitory history, rarely more than 12 months, though the lesion has in all probability been long existent. This at least we may judge to be so in view of the much longer histories of the cerebral cases, some of which have had irritative symptoms for years before tumor has been suspected. The cerebral tumors also are prone to undergo cystic degeneration (*cf.* Fig. 104), and in a good many instances conditions similar to those just described, namely, a cyst with a cap of tumor, are encountered. Thus:

An Irish laborer (Surg. No. 6422) received a cranial injury in January, 1916, which left him with headaches and some mental symptoms. He was brought to the hospital in March, 1917, with advanced general pressure symptoms and a presumed frontal tumor.

At operation a large gliomatous cyst was found in the left frontal lobe with a mural nodule of considerable size which was removed, so far as could be told, in its entirety, and the cavity was subsequently fixed in formalin. He made a good recovery, but owing to his continued mental symptoms was transferred to the Psychopathic Hospital, and thence to an asylum. He completely recovered, and after a few months was discharged. He changed his residence and was lost sight of.

Seven years later, *i.e.*, June, 1925, as these notes were being made, he reported to the clinic. He had remained perfectly well, and had been earning his livelihood as a laborer in another community. The only evidence of his former trouble that could be detected was the residual optic atrophy due to his original choked discs.

But these tumors are by no means always cystic when encountered at operation. The growth, on the contrary, may have a curious soft gelatinous avascular composition which in later years it has been our custom to suck out with a suction apparatus after taking a fragment for histological verification. Such tumors may be very slow in causing general pressure symptoms. Indeed, in some cases these have never appeared. Thus:

A boy, aged 6 (Surg. No. 576), had been having focal epilepsy involving his left face, hand, and arm for two years preceding his admission in November, 1913. An exploration was advised but refused. The attacks became more marked in the absence of headache and choked disc. He was readmitted in May of 1914, and at operation a soft gliomatous tumor involving and greatly enlarging the lower paracentral convolutions was found. This soft gelatinous mass was excised to a depth of about 2 cm., and a number of radium seeds were implanted. The boy made a perfect recovery and the attacks ceased. He remains well, May, 1925, 14 years since the recorded onset of his attacks, with practically no symptomatic trace of the extirpation.

There are many other examples of this sort in the series which might well be quoted, some of them cases of epilepsy which had existed for a long time before the tumor was exposed at operation. In one of these cases, for example (Surg. No. 13161), the patient had had focal seizures for 16 years before pressure symptoms supervened. An exploratory operation disclosed a wide-spread gliomatous condition of the hemisphere without marked tension. The bone flap was removed and the brain was thoroughly radiated. A contralateral paralysis gradually appeared, and he died three years later, 19 years after the onset of his inaugural epileptiform attacks. Other similar cases in the series have lived equally long without radiation.

13. THE FIBRILLARY ASTROCYTOMAS.—These, the last of the series, are by far the most slow-growing and in all respects the most benign of the gliomas. Their identification, in the process of correlating the clinical records with the histological findings, goes far to explain what in the opening paragraphs of this essay we had set out to determine, namely, the nature of those gliomatous tumors which, because of their unexpectedly long post-operative histories, had been such a mystery.

If we include with them the protoplasmic astrocytomas and oligodendrogliomas which, as we have just seen, are also in themselves fairly innocent lesions, we find that 101 out of the 254 classified tumors, but for the chance of their being unfavorably situated, are relatively inocuous. In other words, from a pathological standpoint about 40 per cent. of all the classified gliomas, a percentage larger than that represented by the malignant spongioblastomas, represent lesions which need not be greatly feared.

A good idea of the cases in this group may be gained from a brief consideration of the seven examples in the Hopkins series, due allowance being made for the mistakes in diagnosis, the imperfect surgical technique and the advanced nature of the symptoms which so largely characterized brain tumor cases in those early days. As will be seen, the lesion in all seven was in the posterior fossa. Tumor was unsuspected in three of them, and misdirected operations were performed; one patient died of meningitis after extirpation of the tumor; five of them were nearly blind at the time of admission.

The first case in the series (Surg. No. 20433), a boy of 8, was admitted in March, 1907, after five months of headache, vomiting, staggering and loss of vision. A suboccipital exploration was made with negative findings other than the demonstration of hydrocephalus. He has since had four other operations because of recurrence of symptoms: in June, 1908, when a gliomatous cyst was first disclosed; in July, 1915, when it was again evacuated; in May, 1917, when the cyst wall was " fixed " with Zenker's fluid; and finally in March, 1925, when for the first time the tumor was actually verified as a fibrillary astrocytoma and a considerable mass of it removed. Meanwhile, the boy has retained such vision as he had on his first admission, sufficient to enable him to get about alone. He has been educated at the Perkins Institute for the Blind; is intelligent, a great favorite with his many friends, and leads a very contented and happy existence now over 18 years since the symptomatic onset of his malady.

The second case (Surg. No. 23869), a man of 26, who entered in April, 1909, gave a history of four years of periodic suboccipital headaches and dizziness. He had previously been subjected to a craniotomy for a supposed cerebral tumor. A suboccipital operation disclosed a cerebellar cyst with a large mural tumor, which was completely removed. He has made a complete recovery, and remains well, except for a permanent impairment of vision. He fortunately retains sufficient sight to support himself as a broom maker, at which trade he works from 8 to 10 hours a day, now 20 years since the onset of his trouble, and 16 years since his operation.

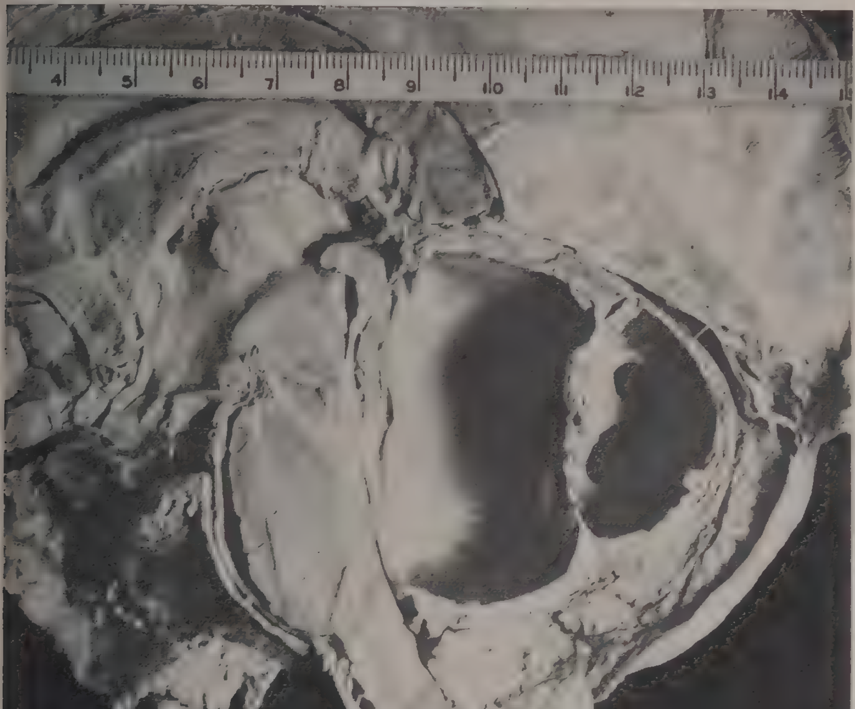

FIG. 105.—J. H. H. Surg. No. 25827. Showing on mid-section, a multilocular cystic astrocytoma fibrillare of the cerebellum unaffected by operation. In one portion of the wall not shown in this photograph is a cap of tumor. (Natural size.)

The third case (Fig. 105) permits us to show one of these cystic lesions *in* *situ,* unaffected by operative intervention. The patient (Surg. No. 25827),* aged 33, was admitted April, 1910, for acromegaly, with the history of two years of headache. His inconspicuous cerebellar symptoms were obscured by his associated malady, and he died following a transphenoidal operation for a pituitary adenoma. The large multilocular cerebellar cyst was an entirely unexpected post-mortem finding. Our later studies of the tissues have disclosed traces of a mural fibrillary astrocytoma.

The fourth case, a child of 6 (Surg. No. 25961), entered May, 1910, with the history of one year of headaches, vomiting and instability, and with complete blindness from a secondary atrophy. At operation a deep cerebellar cyst was found and evacuated. A year later this performance was repeated elsewhere by another surgeon. In December of 1913, the patient entered the Brigham Hospital because of a return of symptoms, at which time a large mural tumor mass partly filling the cyst and weighing 71 grams, was found and removed. Death occurred six days later from a streptococcus meningitis, the only fatality from infection in the entire series of several hundred suboccipital operations at the Brigham Hospital. The orderly who shaved the child came down the next day with scarlet fever. The autopsy showed that the tumor, so far as could be determined, has been completely extirpated.

The fifth case (Surg. No. 26696), a child of 9, totally blind after 8 months of headaches, was supposed to have a cerebellar tumor, but a suboccipital exploration was negative. Death occurred 18 days later, and at autopsy no lesion except hydrocephalus was found. A reëxamination of the tissues in the course of the present study, has disclosed a minute subependymal astrocytoma which blocks the aqueduct of Sylvius.†

The sixth case, a young man of 17 (Surg. No. 28610), had been having periodic attacks of vomiting associated with incoördination of the extremities since he was 4 years of age. In the spring of 1897 these symptoms became exaggerated. In 1904, a small trephine opening had been made over the right cerebellar hemisphere by a surgeon elsewhere. On the day of his hospital admission, October 22, 1911, before a thorough examination had been made, he had a sudden respiratory failure, and after 45 minutes of artificial respiration, on the mere chance of finding a cyst, a needle was introduced through the old trephine opening. It luckily entered a large cyst, on evacuating which there was an immediate resumption of spontaneous breathing. His symptoms completely subsided, and no further operation was undertaken. A year later, very much this same emergency performance was repeated by Dr. C. E. Kahlke, of Chicago. He did well for the next 13 years, when in October of 1924, he was admitted to the Brigham Hospital because of a return of symptoms. For the first time the cerebellum was properly exposed, the large cyst opened, a mural nodule of tumor found and extirpated. He has made a perfect

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* Reported by one of us (Cushing) in "The Pituitary Body and Its Disorders," 1912, Case XXXVIII, p. 195.

† *Cf.* "Notes on a Series of Intracranial Tumors," *Arch. Neurol. and Psychiat.,* 1923, x, Fig. 1.

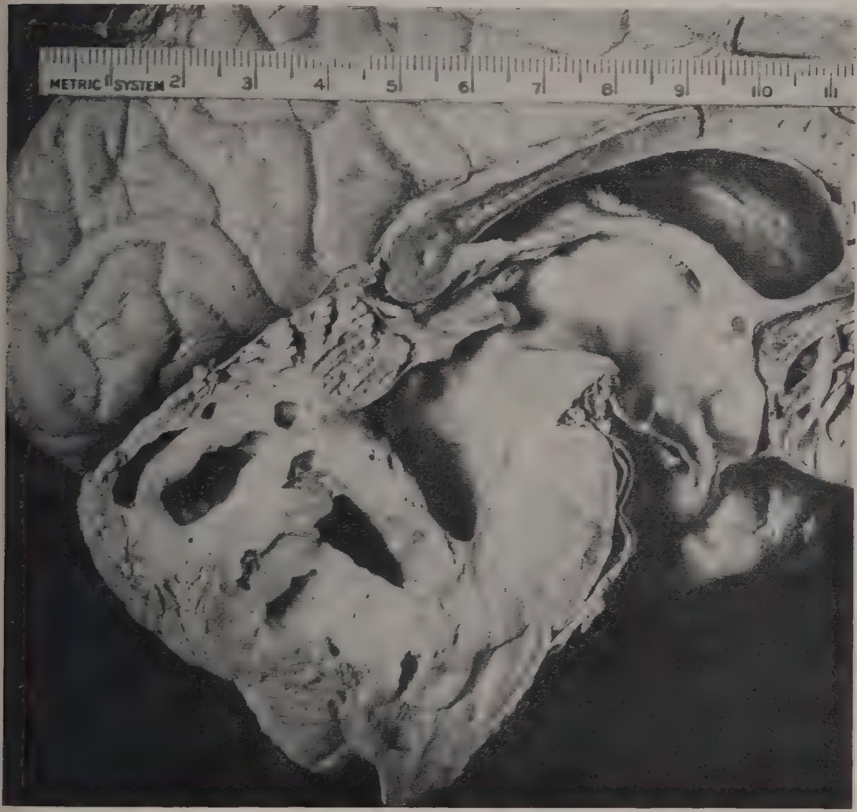

Fig. 106.—J. H. H. Surg. No. 27940. A huge, multicystic, imperfectly demarcated fibrillary astrocytoma shown on mid-section unaffected by operation. Note the dilated aqueduct of Sylvius and proximal portion of the fourth ventricle. Such a tumor, though slow-growing, could hardly be removed in its entirety and it is surprising that the partial removal of such lesions as this is compatible with long duration of life. (Natural size.)

TABLE OF 32 FIBRILLARY ASTROCYTOMAS (1912–1923) CHRONOLOGICALLY ARRANGED.

P. B. B. H. Surg. No.	Date of first admission	Age in years	Previous symptoms in months		Operations. Nature and number	Situation and gross nature of lesion	Survival in months from onset of			Present condition July 1925
			Local	Pressure			Local symptoms	Pressure symptoms	Primary operation	
56	Dec. 1912	4	2	12	I. Dec. 17, 1912. Suboccipital. Cyst evacuated, partial tumor extirpation II. Apr. 2, 1913. Puncture cyst III. May 12, 1913. Puncture cyst IV. May 20, 1913. Partial reëxtirpation tumor and cyst V. May 1920. Ditto (Dr. Elsberg) VI. Oct. 13, 1922. Partial removal solid tumor	Intracerebellar cyst with firm mural tumor	152+	162+	150+	Living 13 years after onset. Has developed dementia precox.
151	June 1913	9	2	18	June 5, 1913. Suboccipital evac. of cyst and excision of firm tumor cap	Intracerebellar multicystic tumor	149+	162+	144+	Living and well after 12 yrs. though nearly blind.
372	Aug. 1913	42	4	66	I. Sept. 9, 1913. Neg. suboccip. exploration and decompression II. Nov. 5, 1914. Reëxploration with evacuation of large cyst	Intracerebellar large multilocular cyst with thin mural tumor	18	80	14	Sudden death 3 wks. after 2nd operation. Autopsy.
1159	Apr. 1914	16	4	2	I. Apr. 27, 1914. Neg. suboccipital exploration II. Jan. 17, 1916. Extirpation tumor	Intracerebellar large firm tumor filling cyst	139+	137+	135+	Living and well over 11 yrs. No residual symptoms. Earning livelihood.
1649	Aug. 1914	38	20	20	I. Aug. 24, 1914. Subtemp. decompression II. Sept. 2, 1914. Neg. suboccipital exploration III. Dec. 4, 1914. Evac. gliomatous cyst	Intracerebellar cyst with mural tumor	150+	150+	130+	Living over 12 yrs. Inmate State Hospital. Psychosis.
4014	Dec. 1915	13	2	18	Dec. 23, 1915. Suboccipital and atlas. Extirpation large tumor	Intracerebellar multicystic tumor over IVth ventricle	19	35	17	Recurrence in 1 yr. No operation. Died May 1917.
4692	May 1916	28	36	36	May 6, 1916. Suboccip. extirpation cap of tumor. Formalin fixation of cyst	Intracerebellar cyst with mural tumor	146+	146+	110+	Living and well over 12 yrs. from onset. Married with children.
5524	Oct. 1916	12	?	11	Oct. 10, 1916. Suboccipital attempted total extirpation	Midcerebellar cystic tumor over IVth ventricle	?	11	0	Postoperative fatality with autopsy.
6150	Jan. 1917	10	12	12	Feb. 1, 1917. Partial enuc. cystic tumor. Zenker fixation	Midcerebellar cystic tumor over IVth ventricle	90	90	78	Survived over 6 yrs. Sudden death Aug. 1923. Autopsy.

10252	Apr. 1919	9	6	18	Apr. 10, 1919. Suboccip. negative exploration	Extensive firm tumor, thalamic region	6	18	0	Fatality 24 hrs. Autopsy.
10619	June 1919	45	72	75	I. June 23, 1919. Suboccip. evac. large cyst. Zenker fixation II. Apr. 15, 1924. Reëxploration evac. cyst with extirp. tumor nodule.	Intracerebellar cyst with mural tumor	145+	148+	73+	Living and well over 12 yrs. from onset. Earning livelihood.
10923	Aug. 1919	33	12	6	I. Aug. 4, 1919. Suboccip. explor. with decomp. after evac. deep cyst II. Dec. 20, 1921. Cyst again evac.	Multicystic tumor rt. temporal lobe	80	74	68	Survived nearly 7 yrs. Death from recurrence. Intervention refused. Autopsy.
13275	Oct. 1920	13	2	10	I. Oct. 16, 1920. Suboccip. neg. exploration II. Mar. 26, 1921. Evac. deep cyst with partial enucleation tumor	Intracerebellar cyst with mural tumor	8	16	6	Sudden death three weeks after 2nd operation. Autopsy.
13661	Dec. 1920	31	3	3	Dec. 20, 1920. Craniotomy; evac. cyst, excision tumor nodule. Zenker fixation	Cerebral pre-central cyst with mural tumor	59+	59+	56+	Living and well over 4 yrs. Occasional focal convulsions. Earning livelihood.
14616	May 1921	14	8	15	June 1, 1921. Suboccip. cyst evac. Excision nodule tumor. Zenker fixation	Intracerebellar cyst with mural nodule	55+	63+	48+	Living and well over 5 yrs. from onset. Attending school.
14879	July 1921	23	2	7	I. July 22, 1921. Subtemp. decomp'n. Evacuation deep gliomatous cyst II. Aug. 11, 1921. Osteoplastic craniotomy. Excision large mural tumor	Right temporal cyst with large mural tumor	50+	55+	48+	Living and well over 4 yrs. from onset. Since married and a mother.
15195	Sept. 1921	12	12	12	Sept. 21, 1921. Suboccip. extirp. large partly cystic tumor	Intracerebellar firm cystic tumor	57+	57+	45+	Living and well nearly 5 yrs. from onset. Attending school.
15378	Oct. 1921	13	?	16	I. Oct. 19, 1921. Suboccip. evac. of tumor-lined cyst. Zenker fixation II. Jan. 1923. Reoperation (Dr. Ernest Sachs) partial removal cyst wall III. Sept. 1923. Puncture (Dr. Sachs) of refilled cyst IV. Oct. 23, 1923. Reoperation (Dr. Sachs) with removal solid mural tumor	Rt. cerebellar cyst with mural tumor	?	61+	44+	Living and well 5 yrs. after onset.
15488	Nov. 1921	10	6	11	I. Aug. 8, 1921. Suboccip. evac. deep cerebellar cyst II. Sept. 14, 1922. Same procedure with partial tumor extirpation III. Jan. 31, 1923. Same. Radical extirp. Formalin fixation cyst	Large cerebellar cyst with mural tumor	53+	58+	47+	Well and at school nearly 5 yrs. from onset.
15933	Jan. 1922	19	3	4	Jan. 21, 1922. Suboccip. evac. glioma-lined cyst; partial removal wall. Formalin fixation	Large cerebellar cyst with mural tumor	45+	46+	42+	Well and earning his livelihood as stenographer nearly 4 yrs. from onset.
16164	Feb. 1922	5	5	6	Mar. 3, 1922. Suboccip. and atlas. Partial removal cystic tumor	Midcerebellar cystic tumor over IVth ventricle	45+	46+	40+	Living and well at school.

TABLE OF FIBRILLARY ASTROCYTOMAS (Continued).

P. B. B. H. Surg. No.	Date of first admission	Age in years	Previous symptoms in months		Operations. Nature and number	Situation and gross nature of lesion	Survival in months from onset of			Present condition July 1925
			Local	Pressure			Local symptoms	Pressure symptoms	Primary operation	
17143	Aug. 1922	21	60	72	I. Oct. 1917. Subtemporal decompression, Chicago II. Aug. 23, 1922. Suboccip. extirp. solid tumor IVth ventricle	Midcerebellar solid tumor over IVth ventricle	60	72	0	Postoperative fatality 8th day.
17892	Dec. 1922	48	84	?	Dec. 12, 1922. Craniotomy, excision large frontal glioma	Frontal lobe solid glioma	114+	?	30+	Well. Occasional focal convulsions. Earning livelihood.
18533	Mar. 1923	34	72	78	I. Apr. 4, 1923. Subtemporal decomp. II. Apr. 16, 1923. Ventricular punct. III. Apr. 17, 1923. Craniotomy. Fragmentary removal large glioma	Paracentral solid glioma	79	85	7	Death 7 mos. post-operative. No autopsy.
18833	May 1923	14	18	4	May 22, 1923. Suboccipital. Partial removal solid glioma. Decompression	Midcerebellar solid glioma over IVth ventricle	44+	30+	26+	Living and well with impaired vision over 2 yrs.
19088	June 1923	30	5	6	I. June 1918. Cranial decompression, France II. Jan. 1919. ditto III. June 30, 1923. Craniotomy with extirpation cystic tumor	Rt. frontal huge cystic glioma	90+	91+	85+	Living and well but not self-supporting. U. S. Army veteran.
19130	June 1923	7	2	4	July 7, 1923. Suboccip. extirp. cystic tumor over IVth ventricle	Midcerebellar cystic tumor	26+	28+	24+	At school free from symptoms over 2 yrs.
19823	Oct. 1923	26	39	?	Oct. 13, 1923. Craniotomy, extirp. by suction of large cystic tumor right temporal lobe	Temporal: soft cystic tumor	42	?	3	Death 3 mos. post-operative.
19941	Oct. 1923	17	12	24	Nov. 12, 1923. Suboccip. evac. glioma-lined cyst. Zenker fixation	Midcerebellar with mural tumor	33+	45+	20+	Living and well nearly 4 yrs. from onset.
20052	Nov. 1923	35	60	36	I. Nov. 19, 1923. Suboccip. exploration negative II. Nov. 21, 1923. Ventriculogram III. Nov. 23, 1923. Ventriculogram IV. Nov. 27, 1923. Left occipital craniotomy. Removal by suction of large soft subcortical tumor	Left occipital lobe solid tumor	80+	56+	20+	Living and well over 6 yrs. from onset.
20153	Nov. 1923	8	1	10	Nov. 30, 1923. Suboccipital extirpation tumor from over IVth ventricle	Midcerebellar large solid growth over IVth ventricle	21+	30+	20+	Living and well; school-child.
20268	Dec. 1923	38	54	?	Dec. 6, 1923. Left craniotomy with decompression. Extirpation firm cystic tumor	Left temporal firm cystic growth	56	?	2	Died 2 mos. later of recurrence.

recovery and bids fair to remain well. It is now *28 years since the onset of unmistakable cerebellar symptoms, and 21 years from the time of his first inadequate operation.*

The last of these seven cases (Surg. No. 27940) was a man of 23, who entered in April, 1912, with a history of intermittent headaches and vomiting for a period of 8 years. Meanwhile, he had become completely blind. It was recognized that he had an internal hydrocephalus, but in the absence of any nystagmus such cerebellar symptoms as he may have had were overlooked or misinterpreted. These were days when callosal puncture was advocated for secondary hydrocephalus, and this procedure was carried out with a fatality three days later. A large multicystic tumor, which proves to be a fibrillary astrocytoma, shown in Figure 106, was an entirely unexpected post-mortem finding.

Between the lines of these abbreviated histories may be read something of the neurosurgeon's errors and successes of the first five years of this work. For the sake of comparison, and as a sample of our assembled data concerning each separate group of the gliomas, the fibrillary astrocytomas from the Brigham Hospital series may be listed here in their chronologically arranged and tabular form. They comprise 32 examples, the patients having come under observation in the ten years between December, 1912, and January, 1924 (the two years of the war excluded).

Though the cases in this later series have by no means all escaped from technical and diagnostic errors, the list shows a great improvement over the earlier series, in which there were 4 post-operative fatalities in 7 cases, whereas there were only 3 in the 32 cases which belong primarily to the Brigham series. Doubtless there will be still further improvement as years go on, now that we have a clearer conception of the behavioristic nature of these lesions.

From this table and from the more detailed notes given for the 7 earlier cases, certain facts concerning these fibrillary astrocytomas may be culled. The average age of the patients on admission was 23 years, and the average age at the onset of symptoms about 3 years younger. The youngest case was 4 when admitted, in 1912, and is now living 13 years later. The oldest case was 48 on admission, in 1922, and is living, nearly 10 years from the onset of his symptoms. By decades the cases run: for the 1st, eleven cases (all cerebellar but one); for the 2nd, eleven cases (all cerebellar); for the 3rd, seven cases (five of them cerebellar); for the 4th, seven cases (three of them cerebellar); and for the 5th, three cases (two of them cerebellar). On the whole, therefore, the cerebral cases are more likely to be found in older patients.

The average duration of pressure symptoms (when recorded) preceding admission and primary operation for the whole series has been 26 months, and for local symptoms (when recorded), 20 months. Due to the preponderance of cerebellar cases in the series, posterior headaches with periodic vomiting has characterized the majority of these slow-growing lesions often antedating by several months anything that, from the history at least, might be interpreted as of definite localizing value. Many of the patients had been long regarded as having some gastrointestinal disorder; and had they been subjected sooner to a neurological examination, localizing symptoms might have been recognized at a much earlier date.

In the ten cerebral cases taken by themselves, the figures are reversed because of occasional focal epilepsy of long standing—indeed no pressure symptoms may have appeared at all (*e.g.*, Cases Nos. 17892 and 20268). In these 10 cases the average duration of antecedent local symptoms has been 34 months, compared to 17 months of recorded pressure symptoms, *i.e.*, headache and visual disturbance. Fortunately in only one of the Brigham cases had the existent choked disc advanced to near blindness, a fact which speaks well for the increasing alertness of the profession in diagnosing brain tumors in general.

Not only has our diagnostic facility improved, but there has been, generally speaking, a corresponding improvement during the past ten years in the surgical treatment of these lesions. The 7 cases in the Hopkins series showed, for 17 operations, many of them misdirected, a 24 per cent. operative mortality and a 57 per cent. case mortality. In the 32 cases of the Brigham series, on the other hand, there have been 58 operations and only 3 post-operative fatalities, giving an operative mortality of 5.2 per cent., and a case mortality of 9.4 per cent. Only one of these fatalities was due to a mistaken localization; the others occurred after the attempted extirpation of tumors overlying the fourth ventricle.

The average post-operative duration of life of the 39 cases has been 54+ months from the first operation. If we exclude from this calculation the cases that died in consequence of an operation, the survival period averages 70+ months. In other words, that these patients should have lived an average of nearly six years since they first came under surgical treatment, emphasizes the comparatively benign nature of the pathological lesion. This would be even more striking were the cases from the later series given a longer time, for the later operations have on the whole been far more radical and better conducted.

An impression which has prevailed in the clinic, that the fibrillary astrocytomas originating in the cerebrum are much less favorable than those found in the cerebellum, is supported by the figures. Thus, in two of the three temporal lobe tumors (Surg. Nos. 19823 and 20268) and in the paracentral tumor (Surg. No. 18533) symptoms recurred rapidly with death in a few months. This, however, depends somewhat upon the gross character of the lesion, in other words, upon whether it has become largely cystic; for in one of the temporal cases (Surg. No. 14879) a mural tumor was enucleated from a cyst, as has been possible in so many of the cerebellar cases, with apparent cure, and another patient (Surg. No. 10923) survived six years and more after mere evacuation of the cyst (Fig. 107).

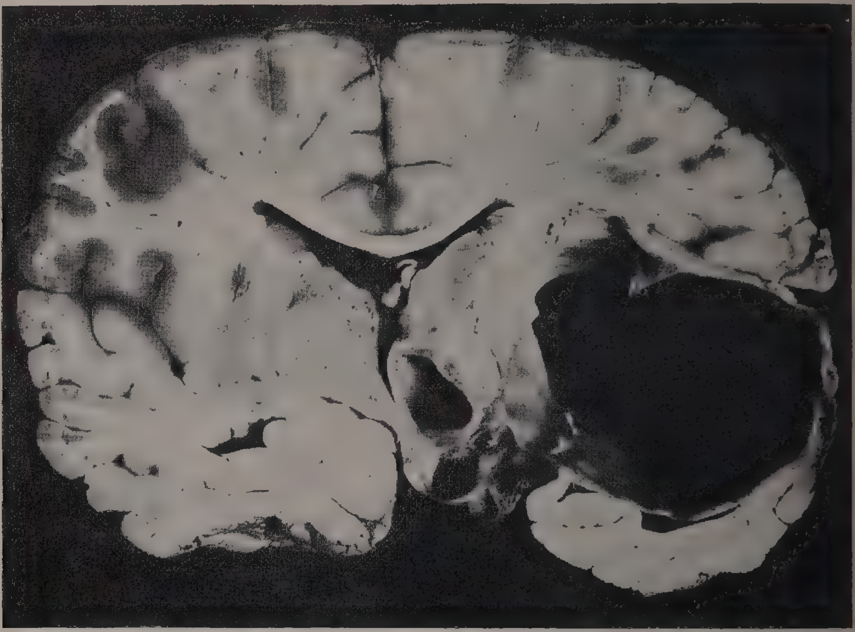

FIG. 107.—Cystic astrocytoma fibrillare of right temporal lobe (Surg. No. 10923). Patient, aged thirty-three, entered August, 1919, after twelve months of "dizzy attacks" (uncinate?) and six months of headache, diplopia, and partial homonymous hemianopsia. A right subtemporal decompression disclosed on puncture of temporal lobe a deep cyst in region suspected. Relief for two years. Cyst again evacuated December, 1921, for return of symptoms. Complete relief another two years when recurrence of same symptoms. Further operation refused. Death April, 1925. Autopsy. Note the multicystic portion of tumor in hypothalamic region. (Two-thirds natural size.)

Though on the whole the cerebellar astrocytomas appear to have undergone cystic changes more often than those of the cerebrum, this impression may have no basis in fact. For comparison with Figure 105, in which a cerebellar tumor was almost wholly cystic, and with Figure 106, in which it was multicystic, the lesion from another autopsy specimen may be shown (Fig. 108), in which six years after a primary suboccipital operation a solid tumor was found at autopsy.

When a suboccipital operation, abandoned merely as a decompression after the disclosure of a subcortical cerebellar cyst, leads to an unexpectedly long survival, with reasonable assurance one can count upon the presence of a fibrillary astrocytoma; and should a secondary operation be called for, a favorable outcome may be anticipated.

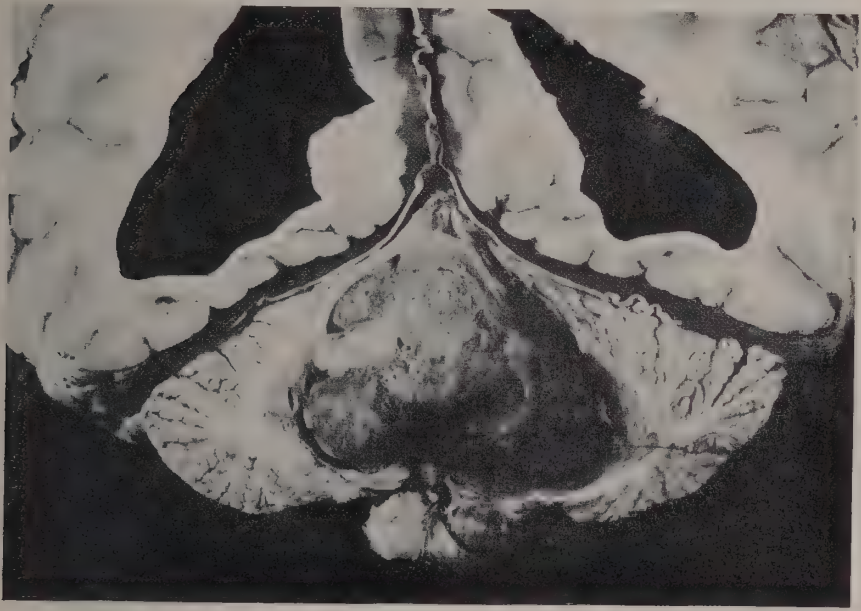

FIG. 108.—Brain of child (Surg. No. 6150) showing solid, recurrent fibrillary astrocytoma six years after original partial enucleation. Sudden death following convulsion. Note apparent enucleability of lesion and marked ventricular hydrops. (Natural size.)

SUMMARY AND CONCLUSIONS

The cerebral gliomas which represent about 42 per cent. of all intracranial new growths in a series comprising something over 1,000 examples, have heretofore been generally regarded as hopelessly malignant tumors.

Impressed by the fact that many patients with tumors of this sort have survived for unexpectedly long periods of time after incomplete extirpation of the lesion, it has seemed imperative that these gliomas should be reclassified and a correlated study of their clinical histories made. The information was needed not only for the sake of prognosis, but as a necessary basis for improvement in our operative procedures.

Such a classification has been undertaken and the attempt made to adopt for these tumors a terminology consistent with that used for the histogenesis and normal structure of the brain. The tissues from 254 of the 414 gliomas in the series up to January of 1924 have been reëxamined by modern histological methods, and have been subdivided into 13 categories.

It has been found, as might have been anticipated, that the tumors whose cells reproduced the structure of the less differentiated cells in the developing central nervous system are more actively growing than are the ones composed of more highly differentiated cells.

Almost half of the reclassified gliomas are of the latter sort, and may be considered to be tumors which, apart from the mischance of their occupying an inaccessible position in the brain or one which leads to serious secondary complications because of cerebrospinal fluid stasis, may be regarded as comparatively benign lesions.

The successive groups of these newly classified gliomas, when arranged in series according to their average survival period, show a variation from those which have few months of life to others which survive, when properly treated, ten years or more; and this lengthened survival period goes hand in hand with the increasing degree of differentiation of the neoplastic cells.

It goes without saying that the more intimate knowledge the surgeon has of the pathology of the lesion with which he is called upon to deal, the more intelligently he will approach his problems. Heretofore, chief stress has been laid by neurologists on the diagnosis and localization of brain tumors, and by neurosurgeons on the technical methods by which they may be exposed. Important as these things are, no less important is a clear understanding of the life-history of the lesions treated, for on this depends more than on anything else the nature of the procedure appropriate to the particular kind of tumor which happens to be disclosed. What is more, with an increase of such knowledge put in application, the nature of the tumor will be actually foretold, before it is exposed at operation, in a constantly increasing percentage of cases.

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